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of Medicine



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Change of address must reach us one month preceding month of issue.

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The American Journal of Medicine

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- Pyelonephritis—An Enigma ROBERT BIRCHALL 501

Clinical Studies

Cat Scratch Disease. A Study of Eighty-Three Cases

W. B. SPAULDING AND JOAN N. HENNESSY 504

An analysis of eighty-three cases of this cause of solitary indolent lymphadenitis, particularly of the axillary nodes, again emphasizes the prevalence of the infection—despite its relatively infrequent diagnosis—and brings out many interesting points about the disease. A skin reaction to the specific antigen remains the most useful confirmatory test, but about half of adults with the infection also give a positive lymphogranuloma venereum complement fixation test. The fever does not respond to antibiotics or other therapeutic measures but the course, fortunately, is self-limited.

Tuberculous Peritonitis. A Study of Forty-Seven Proved Cases Encountered by a General Medical Unit in Twenty-Five Years

W. R. BURACK AND ROBERT M. HOLLISTER 510

As indicated in this analysis of forty-seven cases, the diagnosis of tuberculous peritonitis remains elusive, particularly when it occurs with cirrhosis of the liver. No association of symptoms or signs is reliable, and laboratory confirmation fails in an appreciable proportion of cases. However, in a patient with ascites, with or without cirrhosis, who has unexplained abdominal pain or tenderness, or fever, the possibility of tuberculous peritonitis should be considered, even in the absence of demonstrable tuberculosis elsewhere. Suggestive findings in the ascitic fluid include a total protein content greater than 2.5 gm. per cent and more than 250 leukocytes per cu. mm. with a preponderance of lymphocytes.

An Experimental Malabsorption Syndrome Induced by Neomycin

EUGENE D. JACOBSON, ROBERT B. CHODOS AND WILLIAM W. FALOON 524

The familiar gastrointestinal effects of neomycin include a temporary state of malabsorption. The close resemblance of the broad spectrum of malabsorptive errors so produced to non-tropical sprue is brought out in this paper which describes reduced absorption from the gut of carotene, glucose, D-xylose, iron-59 and vitamin B₁₂, and a fall in serum cholesterol. By comparison with the effects of magnesium sulfate and castor oil it is made clear that the neomycin effects are not attributable simply to hypermotility of the bowel; nor, apparently, to changes in the bacterial flora of the intestines or poisoning of intestinal enzymes required for absorption. The authors favor the hypothesis that the drug induces inflammatory effects in the small intestinal mucosa which obstruct absorption.

Contents continued on page 5



Photos Courtesy F. C. Gindhart, M.D.

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The Differential Effect of Drugs on the Proximal and Distal Colon

SIDNEY FINK AND GERALD FRIEDMAN 534

Registration of intraluminal pressures simultaneously in proximal and distal segments of the colon, before and after injection of appropriate drugs, gave additional evidence that the proximal (vagus innervated) and the distal (sacral innervated) halves of the colon are functionally distinct units. This concept deserves more attention in relation not only to the action of drugs but also in respect to the pathogenesis and course of colonic diseases.

Erythrocyte Dynamics in Liver Disease CHARLES A. HALL 541

There is a good deal of uncertainty concerning the state of the red cell volume in patients with cirrhosis and other liver diseases, since measurements have ranged from low to normal to high, and also little clarification of the several factors which determine the red cell volume under these circumstances. The present study employs appropriate technics and calculations to measure the total red cell volume (found to be low in very few cirrhotic subjects), red cell life span (usually more or less reduced), the rate of red cell production (normal or increased). On the whole, then, this group of subjects with cirrhosis and other liver disorders managed to maintain normal or essentially normal erythrocyte dynamics.

A Rapid Screening Test for Deficiency of Plasma Ceruloplasmin and Its Value in the Diagnosis of Wilson's Disease

PHILIP AISEN, JULIAN B. SCHORR, ANATOL G. MORELL, RUTH Z. GOLD
AND I. HERBERT SCHEINBERG 550

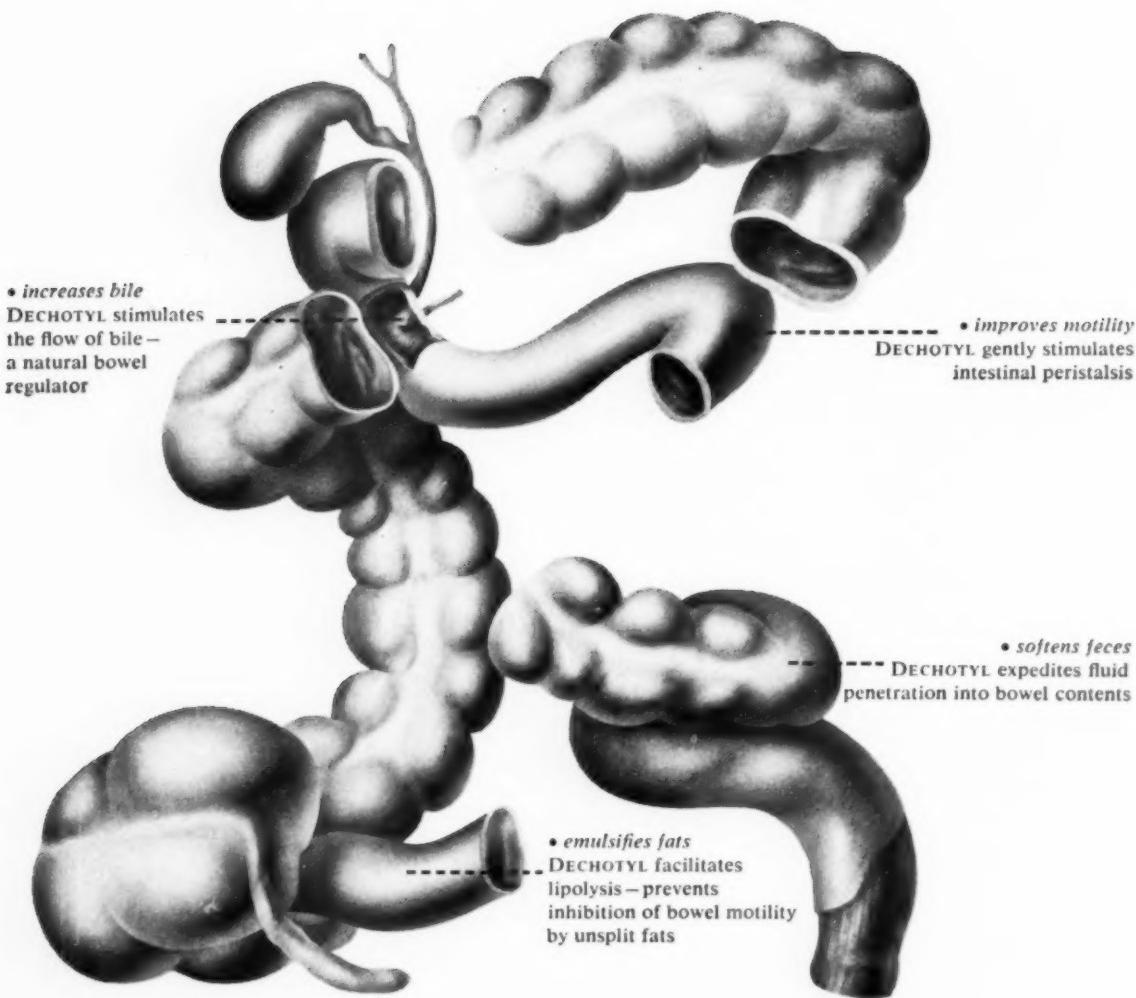
A simple spot test for ceruloplasmin is described, intended to screen children for latent Wilson's disease. There is a practical point involved, since early recognition and institution of preventive measures may obviate the clinical manifestations of hepatolenticular degeneration.

Studies on Copper Metabolism XXIX. A Critical Analysis of Serum Copper and Ceruloplasmin Concentrations in Normal Subjects, Patients with Wilson's Disease and Relatives of Patients with Wilson's Disease

G. E. CARTWRIGHT, H. MARKOWITZ, G. S. SHIELDS AND M. M. WINTROBE 555

Wilson's disease is associated with a disturbance in copper metabolism characterized by deficiency of ceruloplasmin, increased absorption of copper from the gastrointestinal tract, increased non-ceruloplasmin copper in the plasma, and excessive deposition of copper notably in certain tissues of predilection. Which, if any, of these abnormalities represents the primary genetically transmitted defect is still a matter of conjecture. The present study points up discrepancies between the ceruloplasmin concentration and the severity and duration of the clinical manifestations of Wilson's disease—a few patients with overt disease had ceruloplasmin levels within the lowest range of normal, and some symptom-free relatives had distinct ceruloplasmin deficiency. It is concluded that ceruloplasmin deficiency is not the primary metabolic defect in Wilson's disease.

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Reviews

The Closing Mechanism at the Gastroesophageal Junction

GASTON VANTRAPPEN, E. CLINTON TEXTER, JR., CLIFFORD J. BARBORKA
AND J. VANDENBROUCKE 564

While it is apparent that there must be some kind of closing mechanism at the gastroesophageal junction, elucidation of the nature and operation of this mechanism has proved to be extraordinarily difficult. The various proposals made in this connection are here set forth and discussed critically and in detail. It is indicated that a distinct anatomic sphincter, as such, does not exist, yet a physiologic sphincter is readily demonstrable by pressure measurements as a high pressure zone. The possible roles played by a flap-valve, the pinchcock action of the diaphragm and a rosette of mucosal folds are considered.

Gallop Rhythm of the Heart. I. Atrial Gallop, Ventricular Gallop and Systolic Sounds

JOSEPH GRAYZEL 578

An attempt is made in this careful study to correlate gallop rhythm with hemodynamic events of the heart. Gallop rhythm is a mechanical event associated with a relatively rapid rate of ventricular filling and characterized by a ventricular bulge and a low frequency sound. Systolic sounds therefore are not gallop sounds. Two types of gallop rhythm exist, *viz.*, "rapid filling" and "atrial" gallop, both diastolic in time. Cases are presented illustrating the mechanism involved, timing, and the clinical conditions producing these types of gallop rhythm.

Clinicopathologic Conference

Inferior Vena Caval Occlusion 593

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

Acquired Hemolytic Anemia and Transient Erythroid Hypoplasia of Bone Marrow

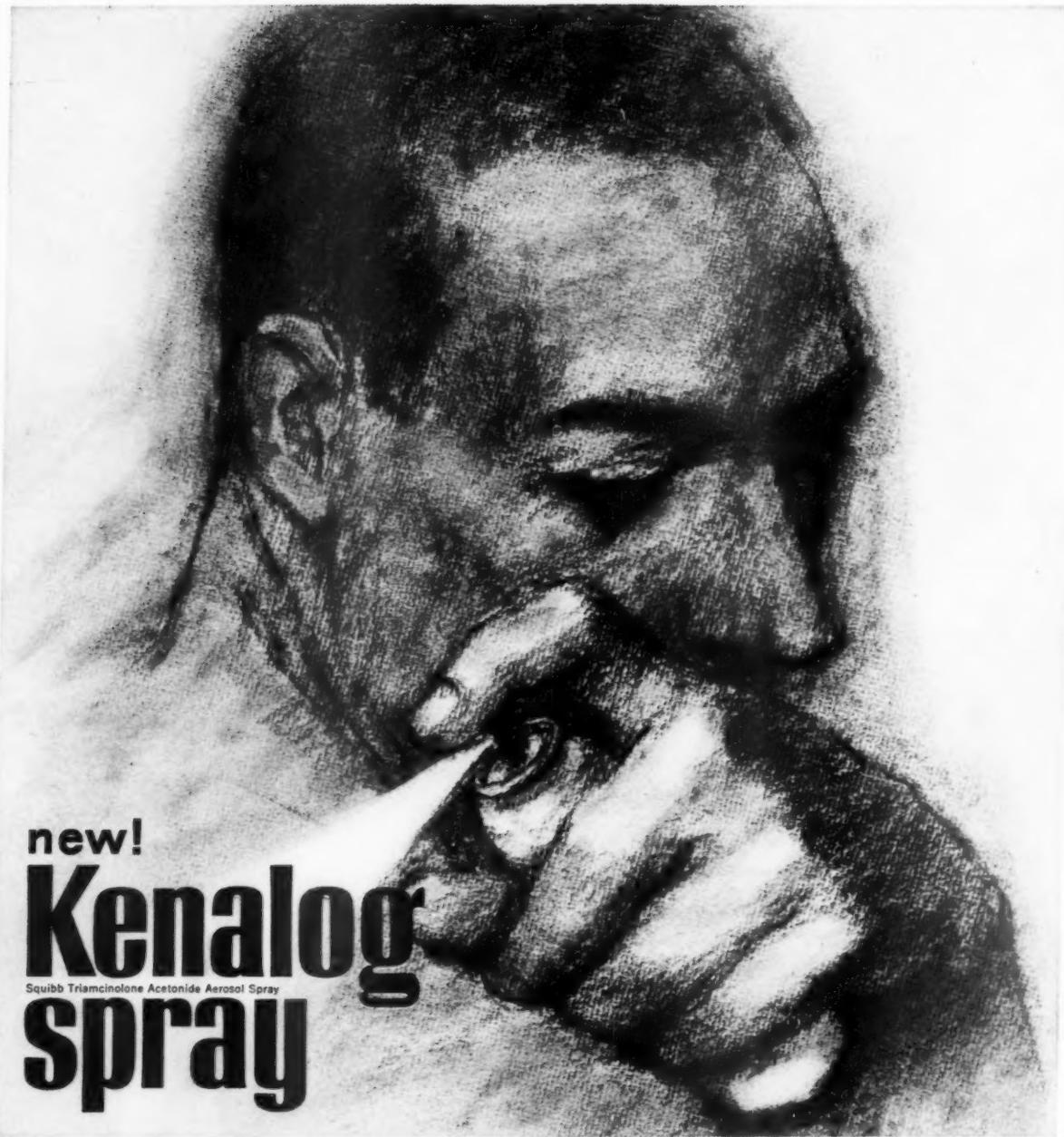
LEO M. MEYER AND ROBERT W. BERTCHER 606

An interesting case.

Elective Thymectomy in the Treatment of Aregenerative Anemia Associated with Monocytic Leukemia 609

A stimulating discussion of the presently confused state of knowledge concerning the possible role of the thymus in the pathogenesis of occasional cases of pure red cell anemia, and the place of thymectomy in management.

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References: 1. Report to the Squibb Institute for Medical Research. 2. Howell, C. M.: Squibb Clin. Res. Notes 1:5 (Oct.) 1958. 3. Goodman, J. J.: Squibb Clin. Res. Notes 1:1 (Oct.) 1958. 4. Smith, J. G., Jr.; Zawissa, R. J., and Blank, H.: Squibb Clin. Res. Notes 1:6 (Oct.) 1958. 5. Fitzpatrick, T. B.; Crowe, F. W., and Walker, S. A.: Squibb Clin. Res. Notes 1:1 (Oct.) 1958. 6. Lerner, A. B.: Squibb Clin. Res. Notes 1:2 (Oct.) 1958. 7. Robinson, R. C. V.: Bull. School of Med., U. Maryland 43:54 (July) 1958.

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- Hypophosphatasia in the Adult J. E. BETHUNE AND C. E. DENT 615

Hitherto described only in children, the authors record the presence of hypophosphatasia in two middle-aged sisters. Both show the characteristic low plasma alkaline phosphatase and urinary excretion of phosphoethanolamine, and interesting skeletal changes consistent with the disorder.

- Hepatolenticular Degeneration. Clinical, Biochemical and Pathologic Study of a Patient with Fulminant Course Aggravated by Treatment with BAL and Versenate

LEO E. HOLLISTER, VIRGINIA L. CULL, VICTOR A. GONDA
AND FELIX O. KOLB 623

An instructive case, well described.

- Pulmonary Thromboarteritis Associated with Interatrial Defect and Rheumatic Carditis SIGMUND L. WILENS AND ERNEST S. REDFIELD 631

An interesting case instructively discussed.

- Primary Hyperaldosteronism without Adrenal Tumor

WALTER MORAN, FREDERICK C. GOETZ, JAMES MELBY,
BERNARD ZIMMERMAN AND B. J. KENNEDY 638

Unequivocal evidence of primary hyperaldosteronism was obtained in an eighteen year old girl with marked hypertension. Surgical exploration, however, failed to reveal adrenal tumor or distinct hyperplasia; nevertheless subtotal adrenalectomy resulted in the return of the blood pressure to normal, and a correction of the metabolic abnormalities. The authors point to other such cases, all in subjects less than eighteen years of age at the time of diagnosis, and suggest that these cases represent a distinct form of congenital adrenal hyperfunction.

- Sheehan's Syndrome with Diabetes Insipidus HAROLD W. EVANS 648

A case illustrating the point that postpartum hemorrhage with circulatory collapse may result in posterior as well as anterior pituitary insufficiency.

- Intrahepatic Cholestasis Following Administration of Chlorpropamide. Report of a Case with Electron Microscopic Observations

JOSEPH REICHEL, STANLEY B. GOLDBERG, MAX ELLENBERG
AND FENTON SCHAFFNER 654

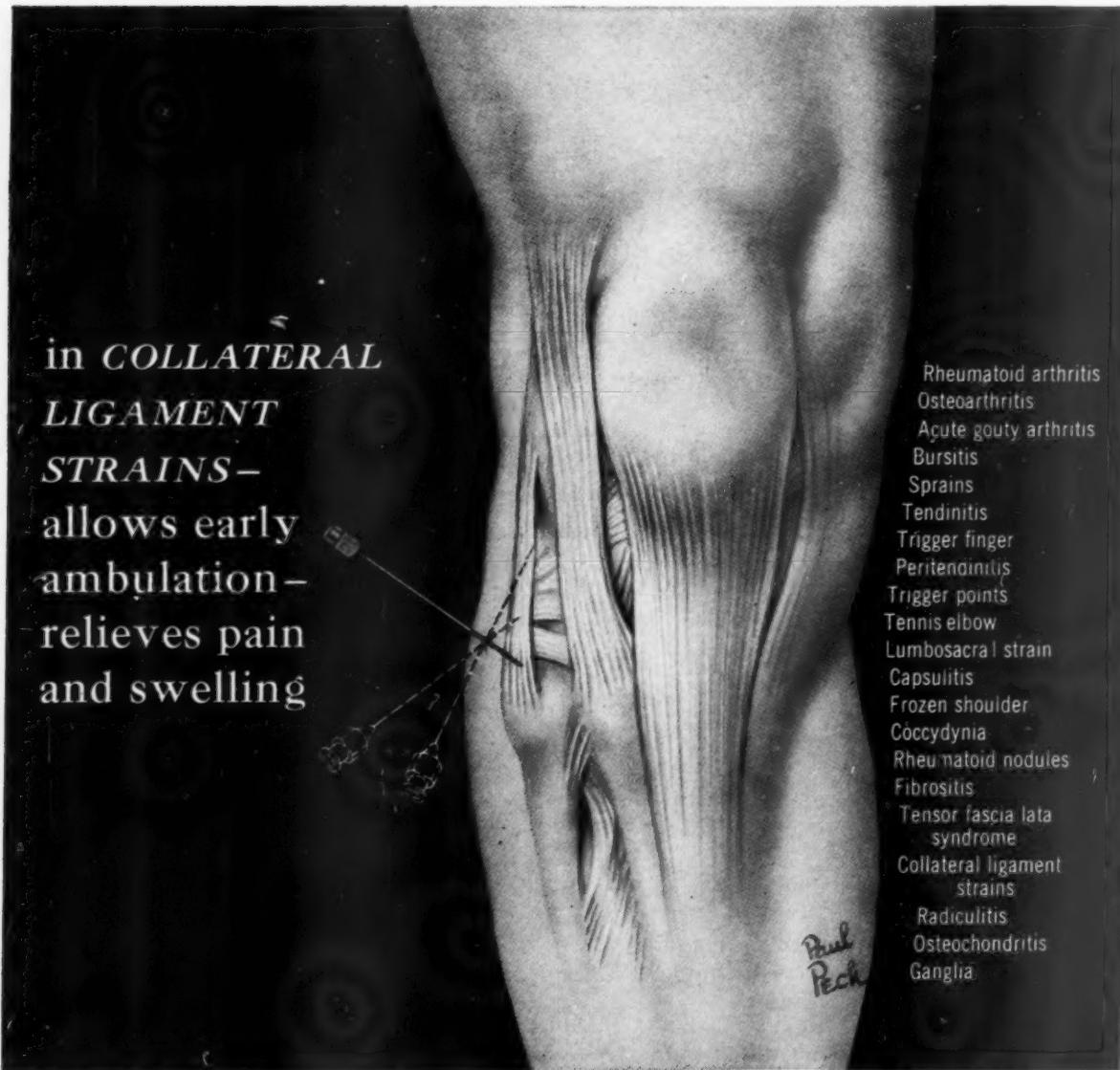
This study adds yet another drug, a sulfonylurea compound, to the list of those causing intrahepatic cholestasis with jaundice.

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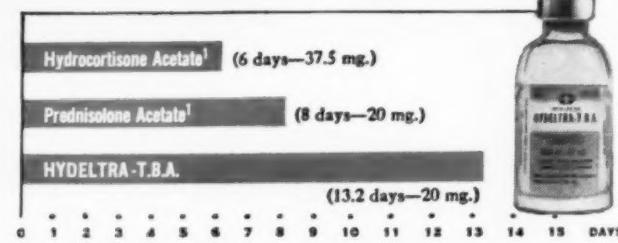
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Lipoid Dermato-Arthritis. Reticulohistiocytoma of the Skin and Joints

JOSEPH ALBERT, WILLIAM BRUCE, ARTHUR C. ALLEN AND HARVEY BLANK 661

An interesting account of an unusual disorder.

Chronic Relapsing Pancreatitis with Extensive Subacute Peritonitis and Chronic, Recurrent Massive "Chylous" Ascites

EARL E. GAMBILL, WALTMAN WALTERS AND PAUL W. SCANLON 668

An instructive case.

PLEASE NOTE . . .

in the article "Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangiolitis). A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients" which appeared on pages 708-729 of the November issue, all alkaline phosphatase values should be read as Shinowara-Jones-Reinhart units rather than Bodansky units as written.

*Advertising Index on Page 161**Change of address must reach us one month preceding month of issue.*

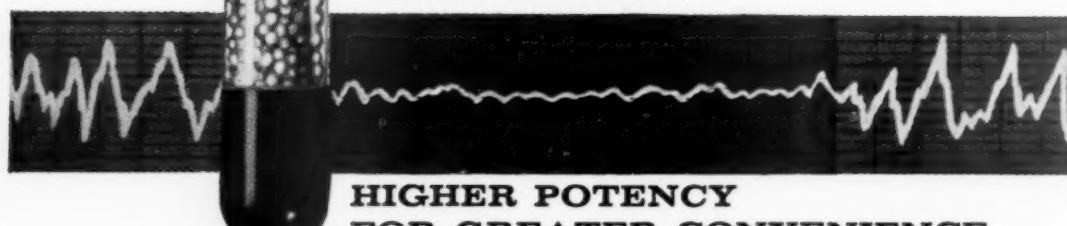
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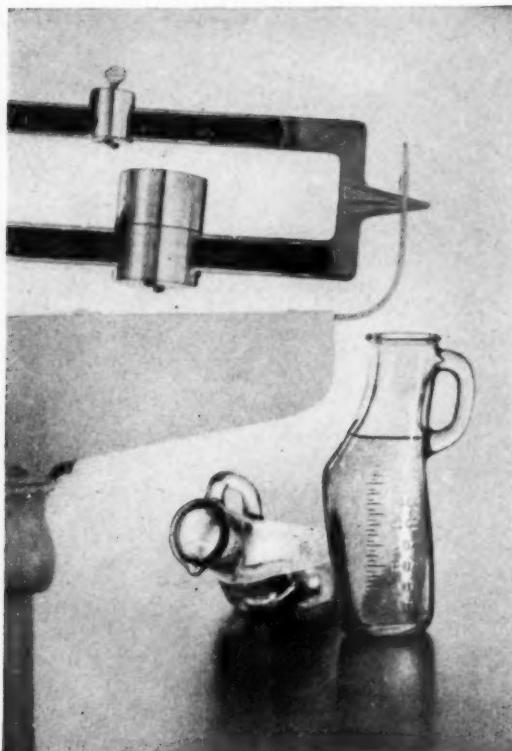
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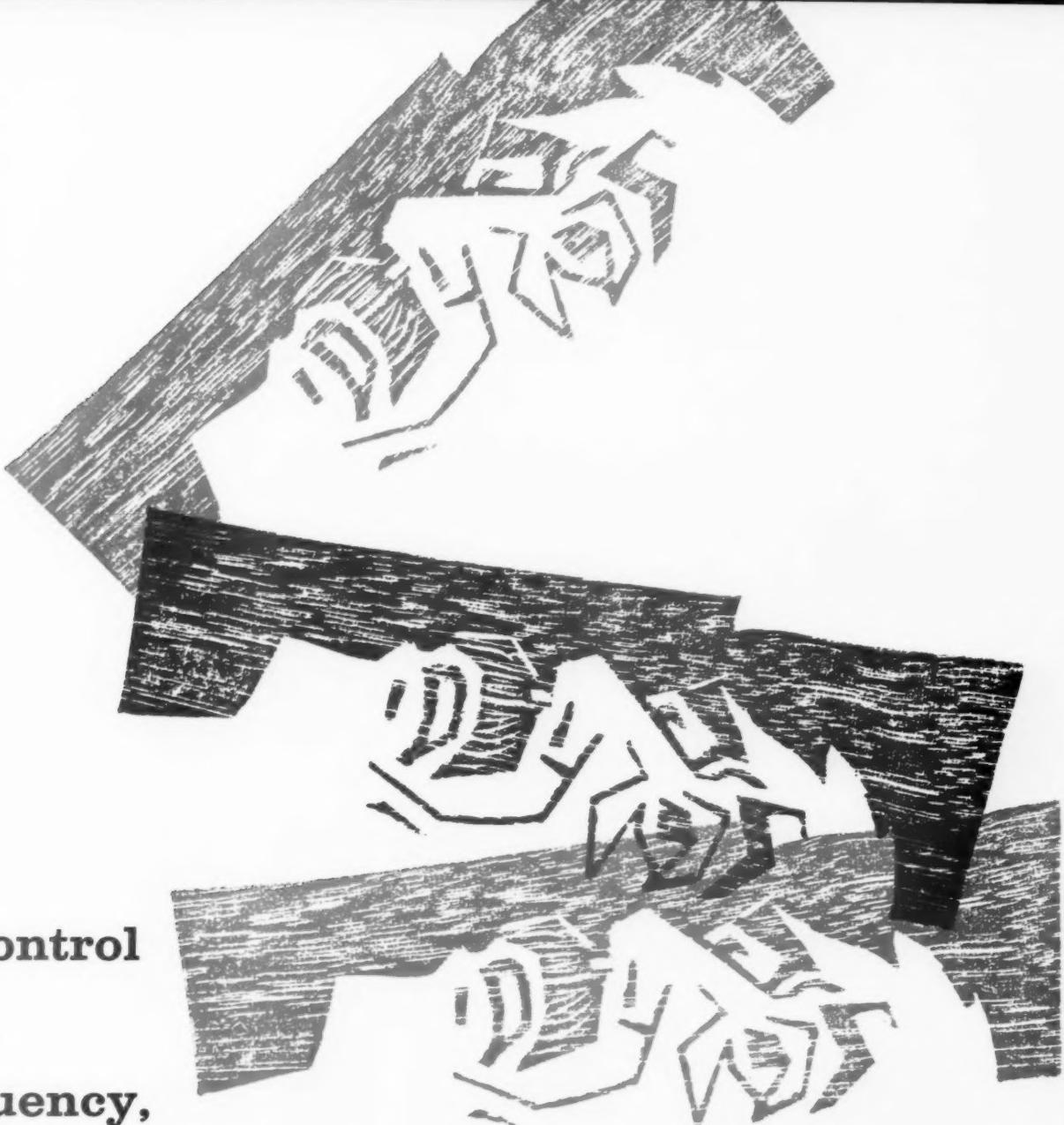
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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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in congestive failure



in hypertension



in premenstrual edema

"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., 59:1769, (May 1) 1959.

"... our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.

"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., 169:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg. tablets DIURIL once or twice a day. Hypertension—One 250 mg. tablet DIURIL twice a day to one 500 mg. tablet DIURIL three times a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide) in bottles of 100 and 1,000.
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hypertension

DIURIL

(CHLOROTHIAZIDE) [®]

than for all other diuretic-antihypertensives combined!



in edema of pregnancy



in cirrhosis with ascites



in renal edema

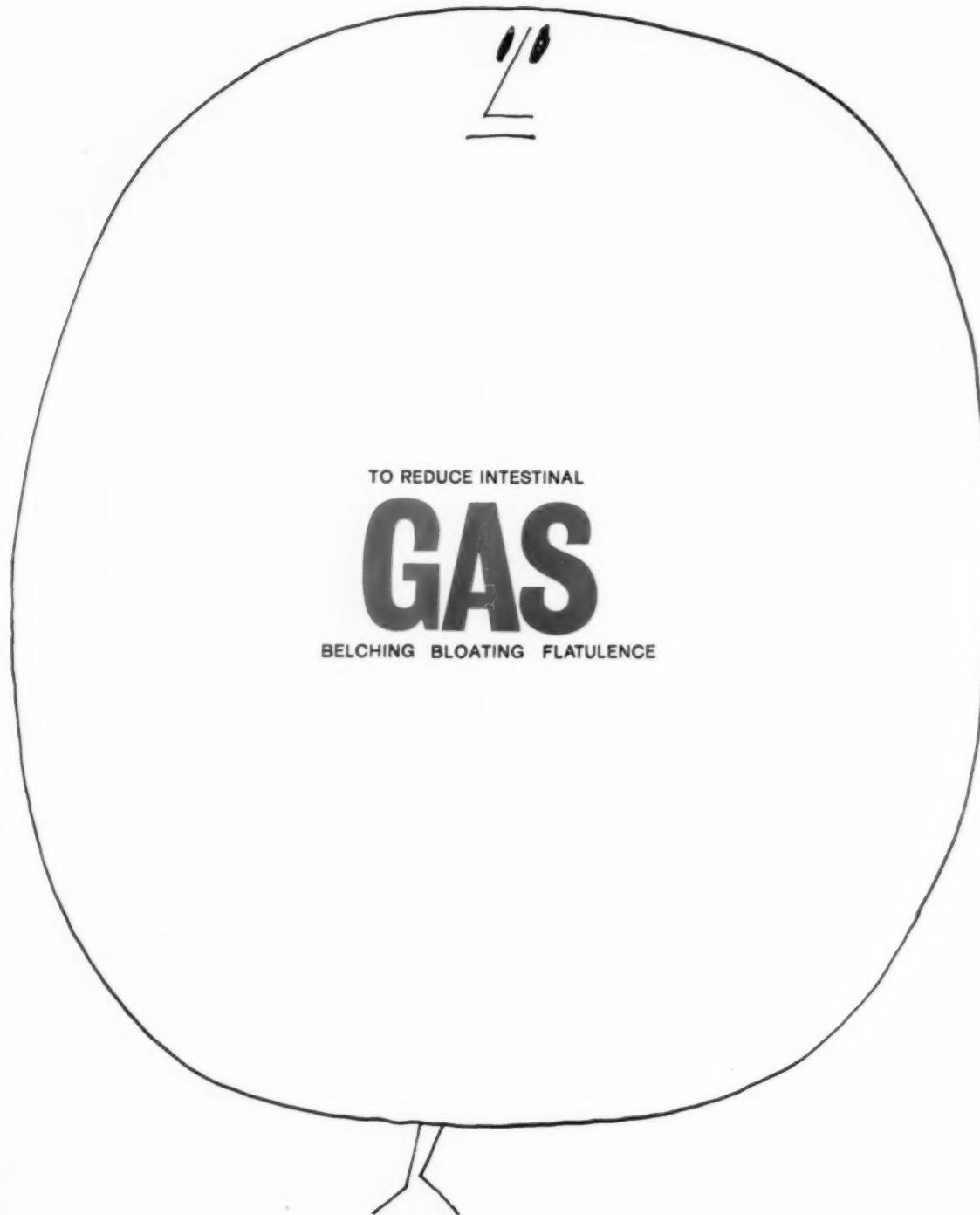
"One hundred patients were treated with oral chlorothiazide." "In the presence of clinically detectable edema, the agent was universally effective." "Chlorothiazide is at present the most effective oral diuretic in pregnancy." Landesman, R., Ollstein, R. N. and Quinton, E. J.: N. Y. State J. Med., 59:66, (Jan. 1) 1959.

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



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TO REDUCE INTESTINAL

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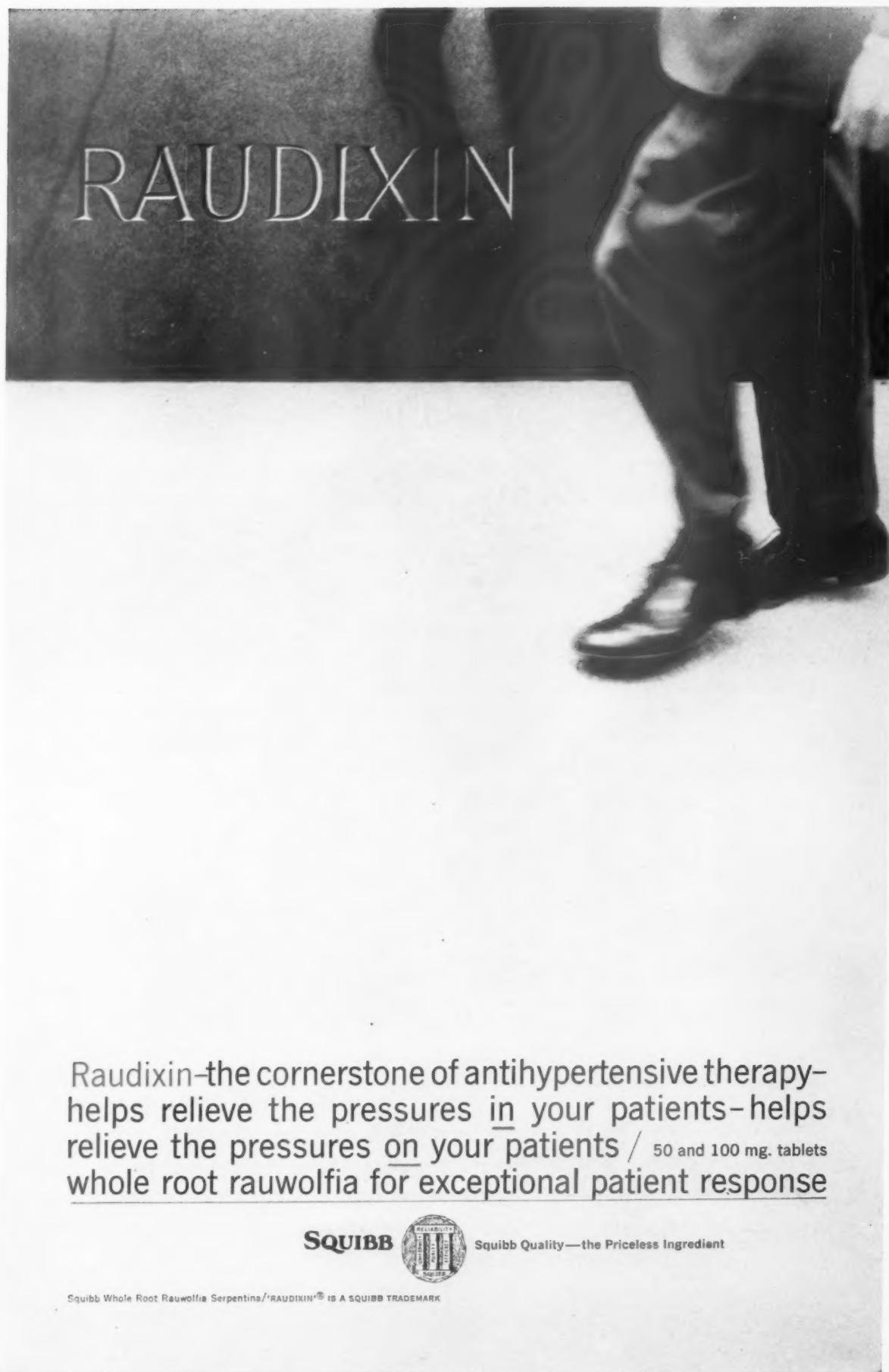
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used to diminish intestinal
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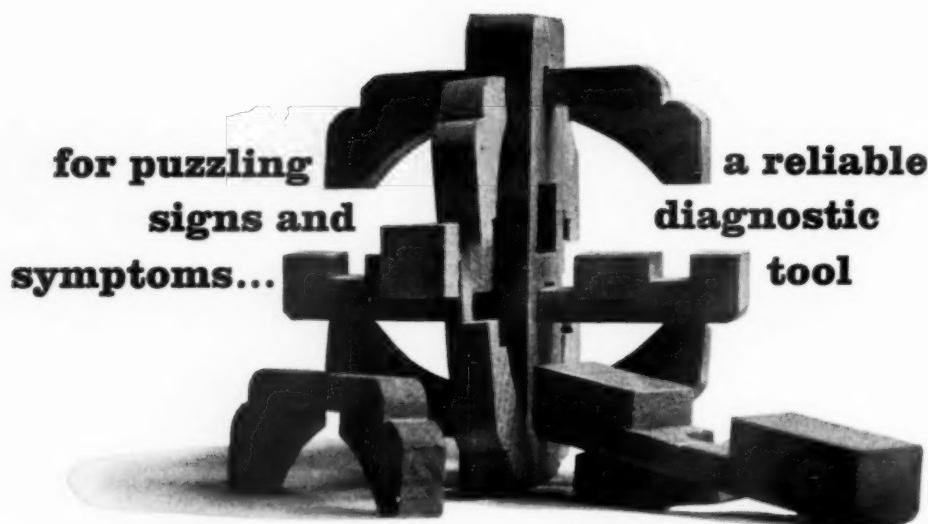
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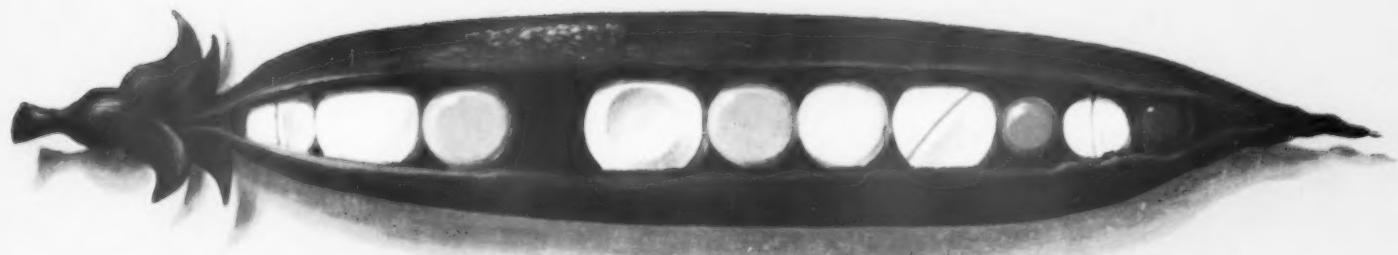
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References: 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:50, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. Scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompui, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

Complete literature and bibliography available on request.



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how does Mellaril differ from other potent tranquilizers?



Mellaril®

THIORIDAZINE HCl

*provides highly effective tranquilization,
relieves anxiety, tension, nervousness,*

but is virtually free of such toxic effects as

jaundice

Parkinsonism

blood dyscrasia

dermatitis



greater specificity of tranquilizing action results in fewer side effects

tranquilization

anti-emetic

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action — divorced from such "diffuse" effects as anti-emetic action.

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specific, effective tranquilizer

"Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines.... This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 100 mg.



**on-the-go relief from
recurrent throbbing headaches**

including migraine syndromes, other vascular headaches, histaminic cephalgia, and occipital neuralgia

Medihaler® Ergotamine

Oral Inhalation of
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Fastest overall method for relieving recurrent throbbing headache

Approximates speed and predictability of relief following ergotamine injection.

Eliminates delay in treatment...Medihaler travels *with* the patient...ready and in use in 5 seconds!

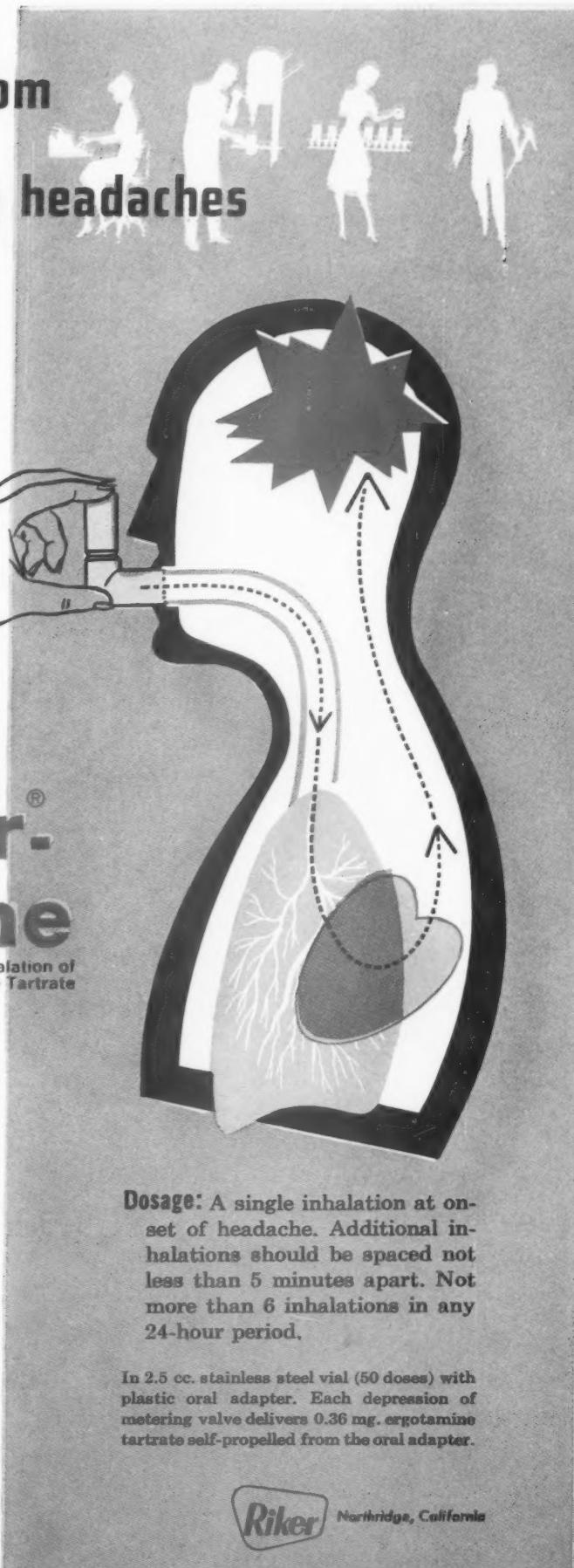
"In a series of over 300 episodes of vascular headache in 41 patients 'Medihaler'-Ergotamine was effective in about 70%."

Graham, J.R.: Faulkner Hospital,
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Dosage: A single inhalation at onset of headache. Additional inhalations should be spaced not less than 5 minutes apart. Not more than 6 inhalations in any 24-hour period.

In 2.5 cc. stainless steel vial (50 doses) with plastic oral adapter. Each depression of metering valve delivers 0.36 mg. ergotamine tartrate self-propelled from the oral adapter.

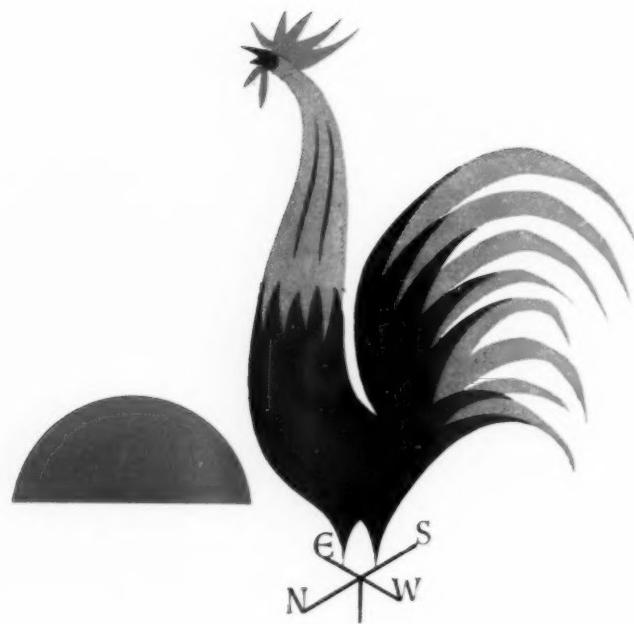
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for morning sickness

brand of meclizine hydrochloride *

Bonine



DOSAGE:
One or two tablets
give 24 hour protection.
Administer at bedtime to
prevent "next morning"
sickness.

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"Also, there are fewer therapeutic failures when patients are treated with . . . [BONINE] than with the other drugs."¹
 "...[BONINE] is highly effective in relieving the nausea and vomiting of pregnancy, providing also the advantage of prolonged action. Thus, patients need not anticipate medication in the early morning hours when nausea is at its worst."²

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"...[BONINE] is a drug which is safe and nontoxic to both the mother and fetus and which is attended by a minimum of undesirable side effects."³

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"The incidence of side effects is very low and this agent exhibits less sedation and somnolence within therapeutic ranges than any of the effective antiemetic agents."¹

"Side effects were conspicuous by their rarity."²

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"The most striking advantage of...[BONINE] was that the administration of an effective dose only once daily, at bedtime, gave 24 hour protection, thus obviating the inconvenience and distress of repeating doses during the day."⁴

"...[BONINE] is especially effective and has the advantages of a long duration of action (up to 24 hours) and a minimum of untoward side reactions."¹

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A single low-dosage drug providing therapeutic benefit at reasonable cost...contains no unnecessary added ingredients that increase cost...requires no extended-action tablet structure for prolonged effect.

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The value of BONINE as an antinauseant has been well documented and is supported by six years of successful clinical use.¹⁻¹⁸

only rarely does one drug meet so well the needs of one condition

REFERENCES: 1. Moyer, J. H.: M. Clin. North America, Mar., 1957, p. 405. 2. Lebherz, T. B., and Harris, J. H.: Obst. & Gynec. 8:606, 1955. 3. Mulherin, C. McL., and Bryans, C. I., Jr.: J. M. A. Georgia 45:46, 1956. 4. Bass, R. F.: Mississippi Doctor 32:176, 1954. 5. Seidner, H. M.: Illinois M. J. 109:20, 1956. 6. Charles, C. M.: Geriatrics 11:10, 1956. 7. Weil, L. L.: J. Florida Acad. Gen. Practice 4:9, No. 3, 1954. 8. Kinney, J. J.: J. M. Soc. New Jersey 53:128, 1956. 9. Semmens, J. P.: Obst. & Gynec. 9:588, 1957. 10. Conner, P. K., Jr., and Moyer, J. H.: GP 14:124, No. 5, 1956. 11. Daeschner, C. W., et al.: South. M. J. 49:1485, 1956. 12. Report of study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755, 1956. 13. Kean, B. H.: GP 20:112, No. 6, 1956. 14. Seppänen, A.: Geriatrics 14:457, 1959. 15. Hardman, E. F.: North Carolina M. J. 20:298, 1959. 16. Master, A. M.: New York J. Med. 58:2712, 1958.

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BONINE Tablets, scored, 25 mg.

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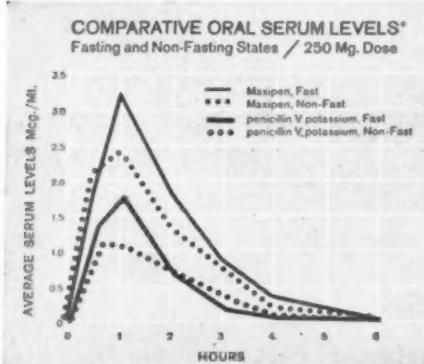
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MAXIMAL ABSORPTION Acid stable, extremely soluble. MAXIPEN is rapidly absorbed from the gastrointestinal tract.

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MAXIMAL FLEXIBILITY May be administered without regard to meals. However, highest absorption is achieved when taken just before or between meals.

MAXIMAL ORAL INDICATIONS Indicated in infections caused by streptococci, pneumococci, susceptible staphylococci, and gonococci, including:

pneumococcal pneumonia	impetigo
gonorrhea	susceptible
tonsillitis	staphylococcal
laryngitis	abscesses (with indicated surgery)
otitis media	cellulitis
streptococcal pharyngitis	lymphangitis
	pyoderma

Also prophylactically in secondary infections following tonsillectomy, dental extractions, other surgical procedures.

Dosage: For moderately severe conditions, 125 to 250 mg. three times daily. For more severe conditions, 500 mg. as often as every four hours around the clock.

Note: To date, MAXIPEN has not shown less allergic reactions than older oral penicillins. Usual precautions regarding administration should be observed.

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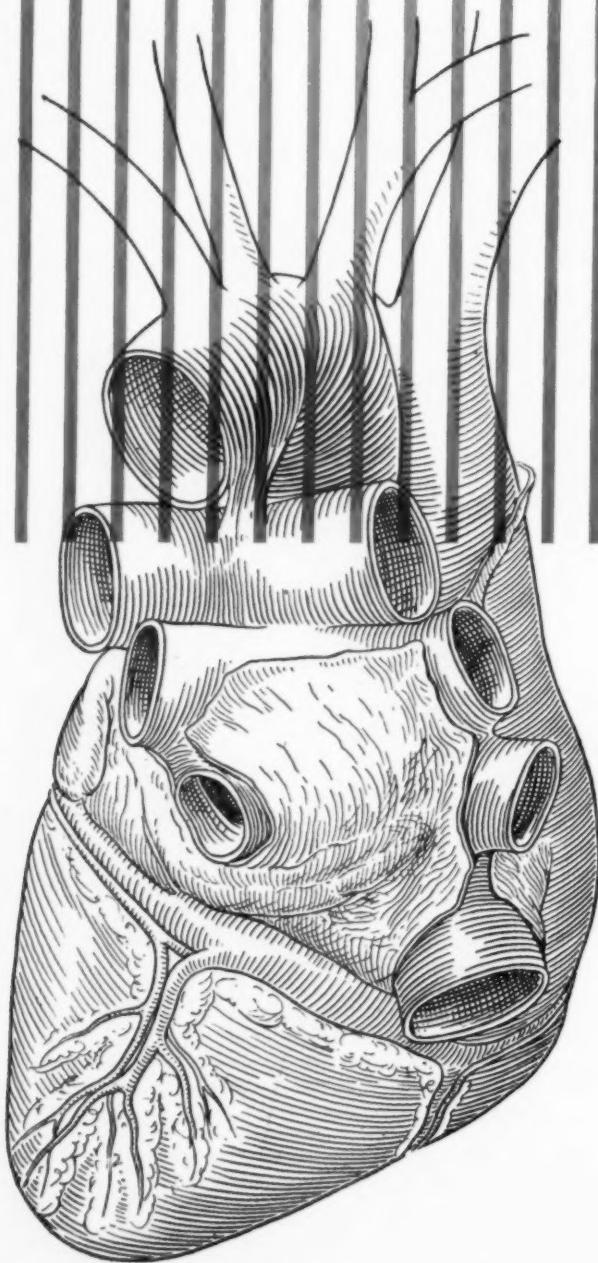
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for total management of angina pectoris

Marplan prevents pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.¹⁻³ To date, Marplan prophylaxis has been evaluated in over 300 angina patients. The response rate was 76 per cent with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.¹ One study reported "excellent effects with relatively small doses" and "greater relief than [with] any other compound in our experience."²

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris and, while it frequently abolishes anginal pain, Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.



with two distinct primary effects, for two indications

Marplan

a happy balance of potency/safety

A broad clinical research program continues to define the full range of Marplan's clinical applicability. However, already some 300 research clinicians have evaluated Marplan in more than 4000 patients in two primary diagnostic categories—*angina pectoris and depression*.

Marplan has been shown to be considerably more active than other amine oxidase regulators. While clinically such increase in potency has heretofore been associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of the side reactions of the hydrazines. Moreover, throughout the extensive clinical investigations, no liver damage has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult complete literature and dosage instructions, available on request, before prescribing.

Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Co-operative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.



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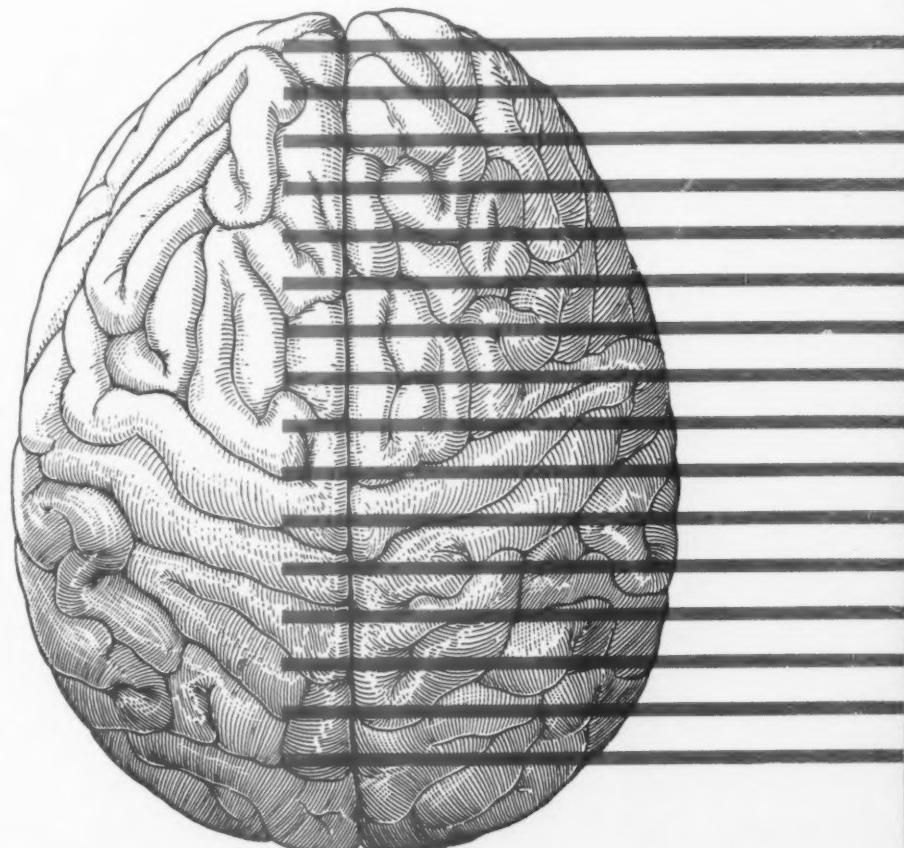
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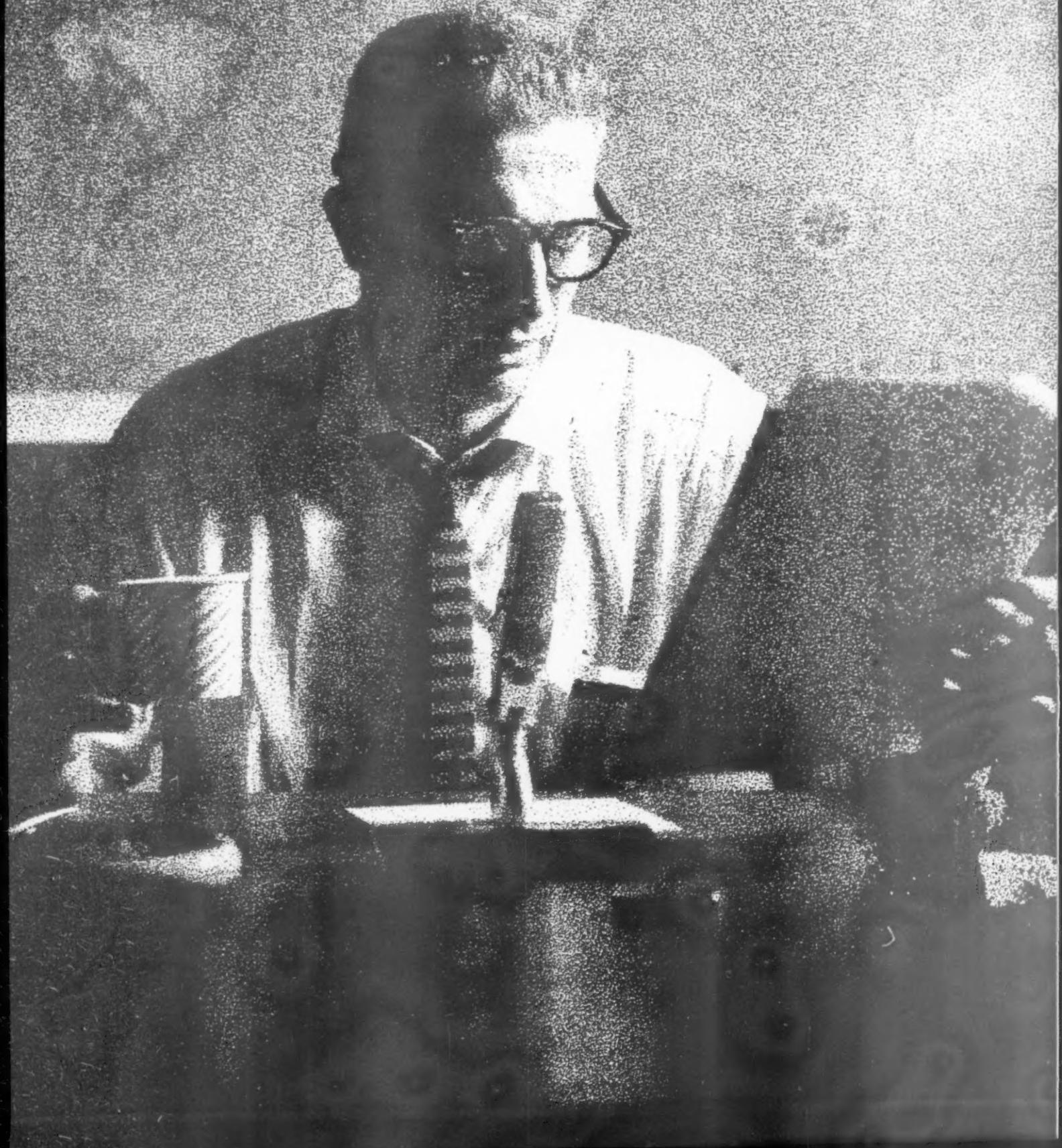
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The value of Marplan in depression: Marplan is indicated in the broad range of emotional and psychiatric disorders with associated symptoms of depression, withdrawal or regression. To date, Marplan has been fully evaluated in more than 3700 patients with depression. The majority (67 per cent) showed significant improvement¹: "Depression of mood and somatic preoccupation were less pronounced, concentration improved, irritability lessened, and the patients appeared to be more relaxed."¹

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*greater flexibility in the control of tension, hypermotility
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PATHIBAMATE-200—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.

Adjust to patient response.

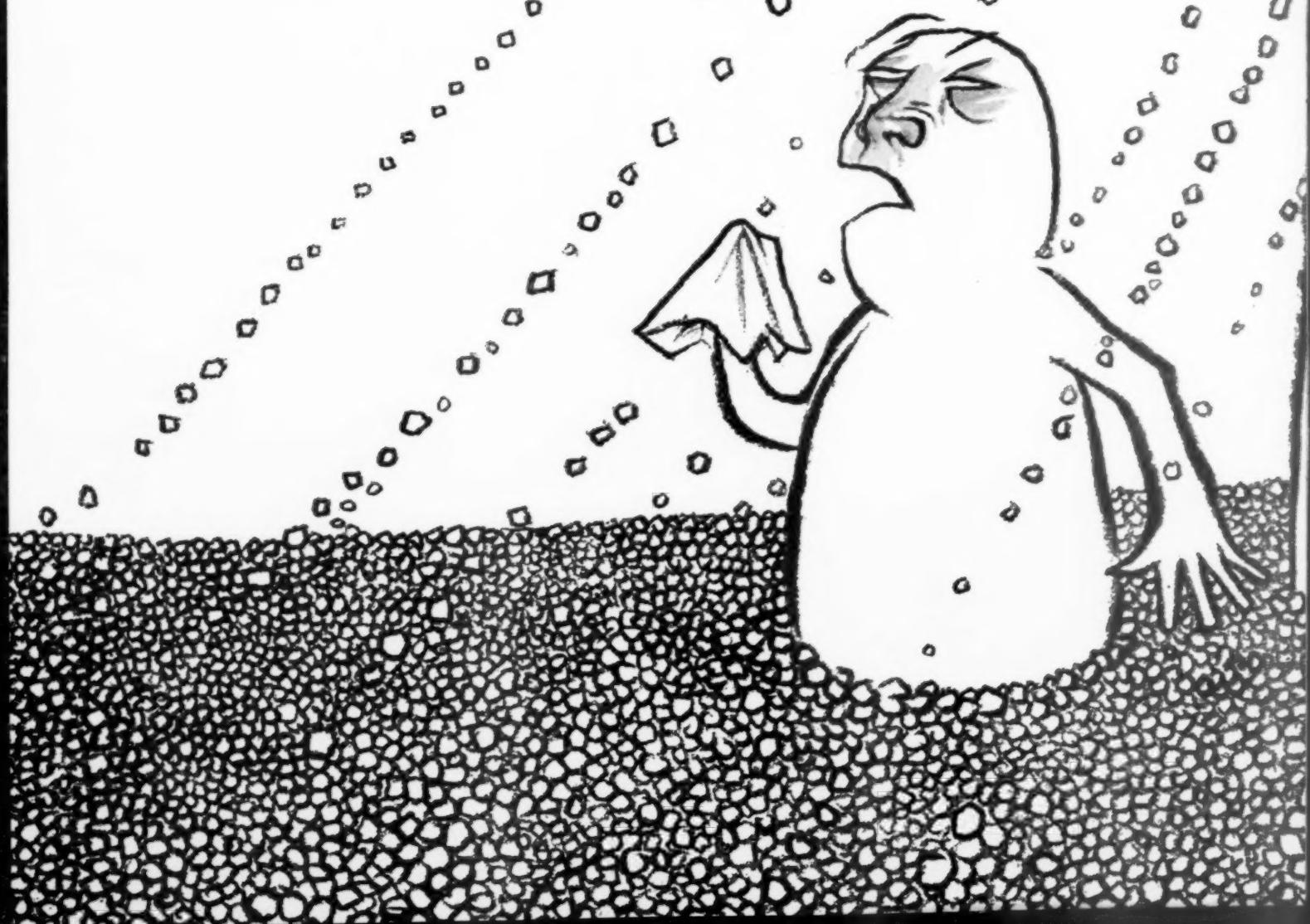
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*Babcock, G., Jr., and Packard, L. A.: *Clin. Med.* 6:985 (June) 1959.

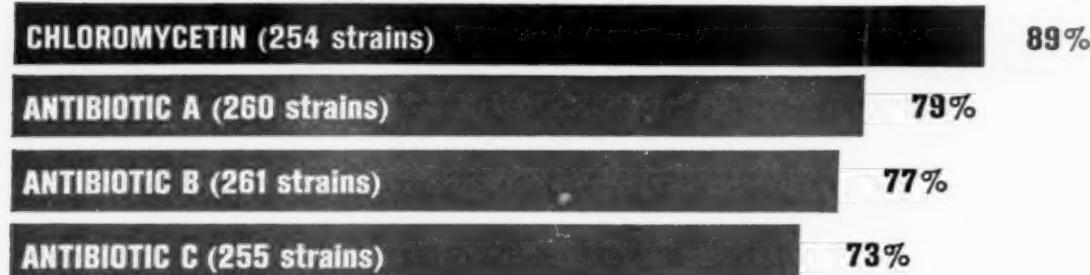
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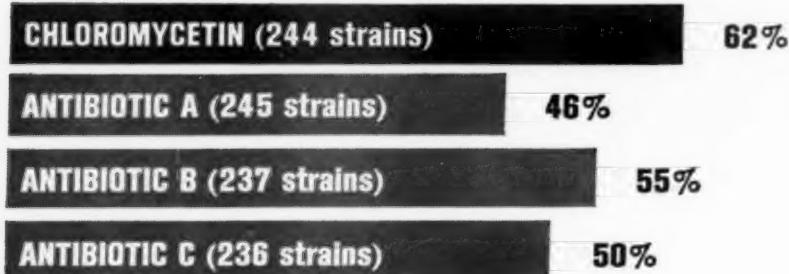
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*Adapted from Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Martí-Ibañez, F.: *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 414.

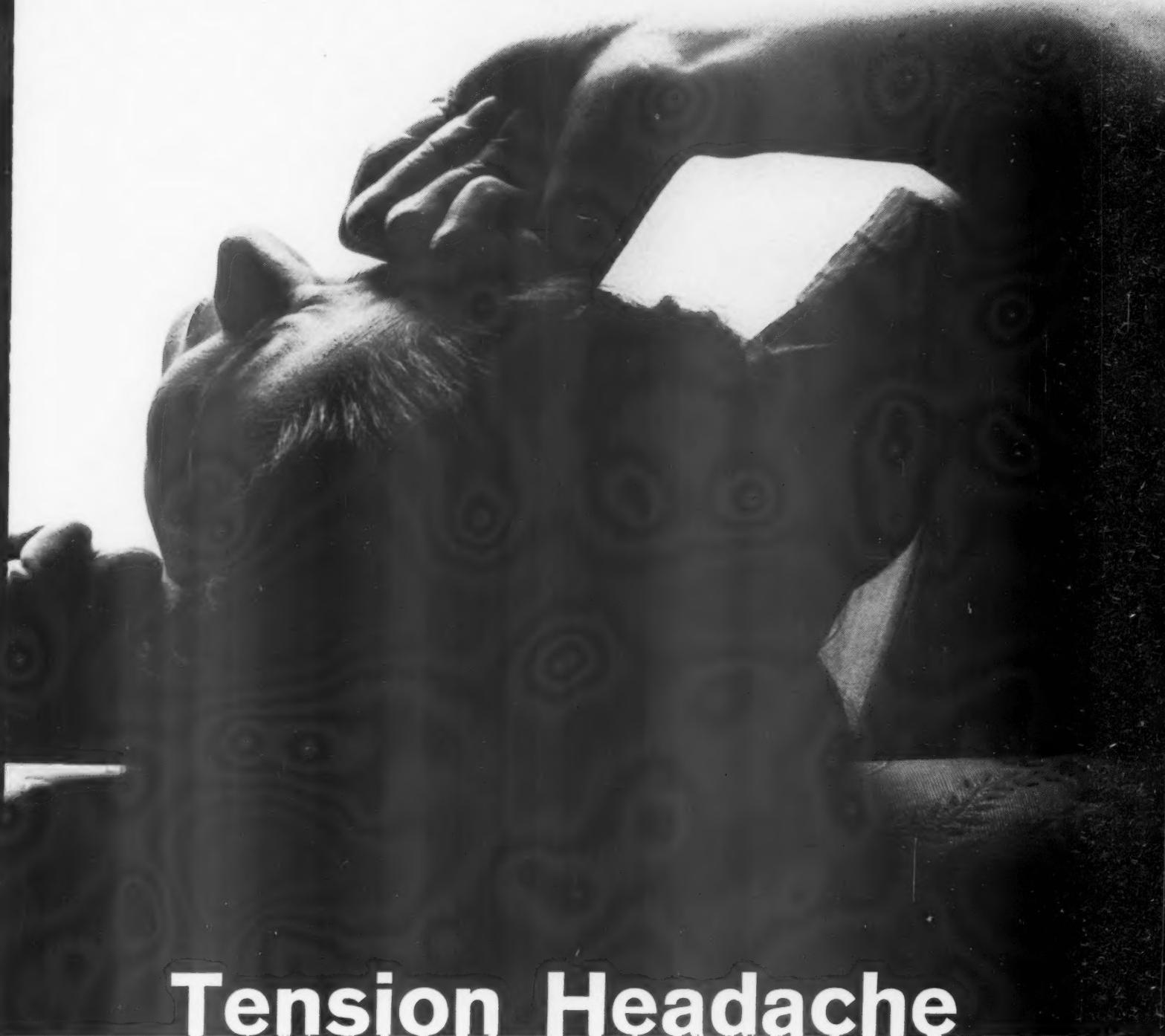
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CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

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Relief without Analgesics

"Meprobamate was found of considerable value in reducing the tension component of chronic headache, and thus decreasing the frequency and severity of attacks. No intolerance, dependence, or side effects were noted. . . ." Blumenthal, L.S., and Fuchs, M.: Am. Pract. & Digest Treat. 9:1121 (July) 1958.

An extensive bibliography attests to the striking effectiveness and noteworthy safety of EQUANIL (meprobamate, Wyeth) in a variety of tension and anxiety states. EQUANIL possesses specific action; pharmacological action is not diffuse. Rapid metabolism precludes cumulative effects.

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relieves both stiffness and pain with safety... sustained effect

In 100 consecutive patients with the low back syndrome, Kestler¹ reported that particularly gratifying was the ability of SOMA "to relax muscular spasm, relieve pain, and restore normal movement, thus speeding recovery in a large majority of the patients."

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EXCELLENT TO VERY GOOD 68 %

GOOD TO FAIR 23.7 %

*Investigators' reports to the Medical Department, Wallace Laboratories. (Total of 278 cases)

NOTABLE SAFETY—extremely low toxicity; no known contraindications; side effects are rare; drowsiness may occur, usually at higher dosage

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SUPPLIED—as white, coated 350 mg. tablets, bottles of 50; also available for pediatric use:
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T. M.
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1. Kestler, O: In The Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959. 2. Berger, F. M.; Kletzkin, M.; Ludwig, B. J.; Margolin, S., and Powell, L. S.: J. Pharm. Exp. Ther. 127:66 (Sept.) 1959. 3. Spears, C. E. and Phelps, W. M.: Arch. Pediat. 76:287 (July) 1959. 4. Phelps, W. M.: Arch. Pediat. 76:243 (June) 1959. 5. Friedman, A. P.; Frankel, K., and Fransway, R. L.: Papers presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959. 6. Kuge, T.: Unpublished reports. 7. Ostrowski, J. P.: Orthopedics (In Press).

Literature and samples on request

Also available on request: The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. (185 pages)

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In Anxiety and Anxiety-induced Depression

"In contrast to other phenothiazines, it [PERMITIL] mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."¹

- In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.²
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- Patients become calm without being drowsy and normal drive is restored.
- Onset of action is rapid; effect is prolonged.
- PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

SUPPLIED: Tablets, 0.25 mg., bottles of 50 and 500.

REFERENCES: 1. Ayd, F. J., Jr.: Current Therapeutic Research 1:41 (Oct.) 1959.
2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.



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The beneficial effects of a single dose persist for at least 4 hours—therefore for most patients q.i.d. dosage is highly satisfactory.

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Response of patients treated in various clinical studies¹ to date was 85 per cent good, 7 per cent fair, and 8 per cent unsatisfactory.

4 unusual safety

The only side effect reported has been transitory, easily controlled headache, normally considered an expression of effective pharmacodynamic activity.²

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of emetic situations without
antihistamine side effects and
without phenothiazine risks**

of the antihistamines.⁶⁻⁹ No sedation or other side effects were observed in TRAVEL SICKNESS patients, who were quickly and efficiently relieved by Tigan.¹⁰ Nor was any drowsiness or other untoward reaction seen in 16 PREGNANT women, 15 of whom became asymptomatic on Tigan, while other antiemetic medication had failed or caused drowsiness in several.¹⁰ In GASTROINTESTINAL vomiting, where results were "good" in 86 per cent and "fair" in 14 per cent, Tigan was "well tolerated" by all.¹¹

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Medication	Number of Patients	RESULTS	
		Improved	Unimproved
Tigan, given initially	142	133	9
Placebo, given initially	74	7	67
Tigan, given after failure of placebo	65	61	4

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For dosage instructions, consult product literature available on request.

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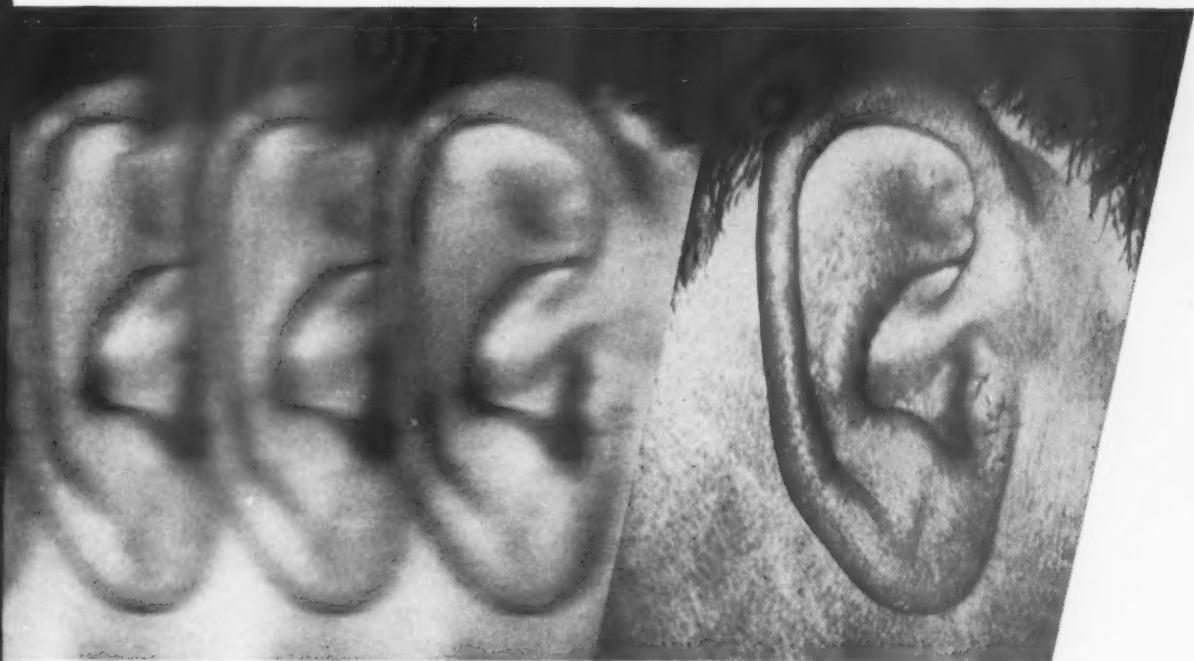


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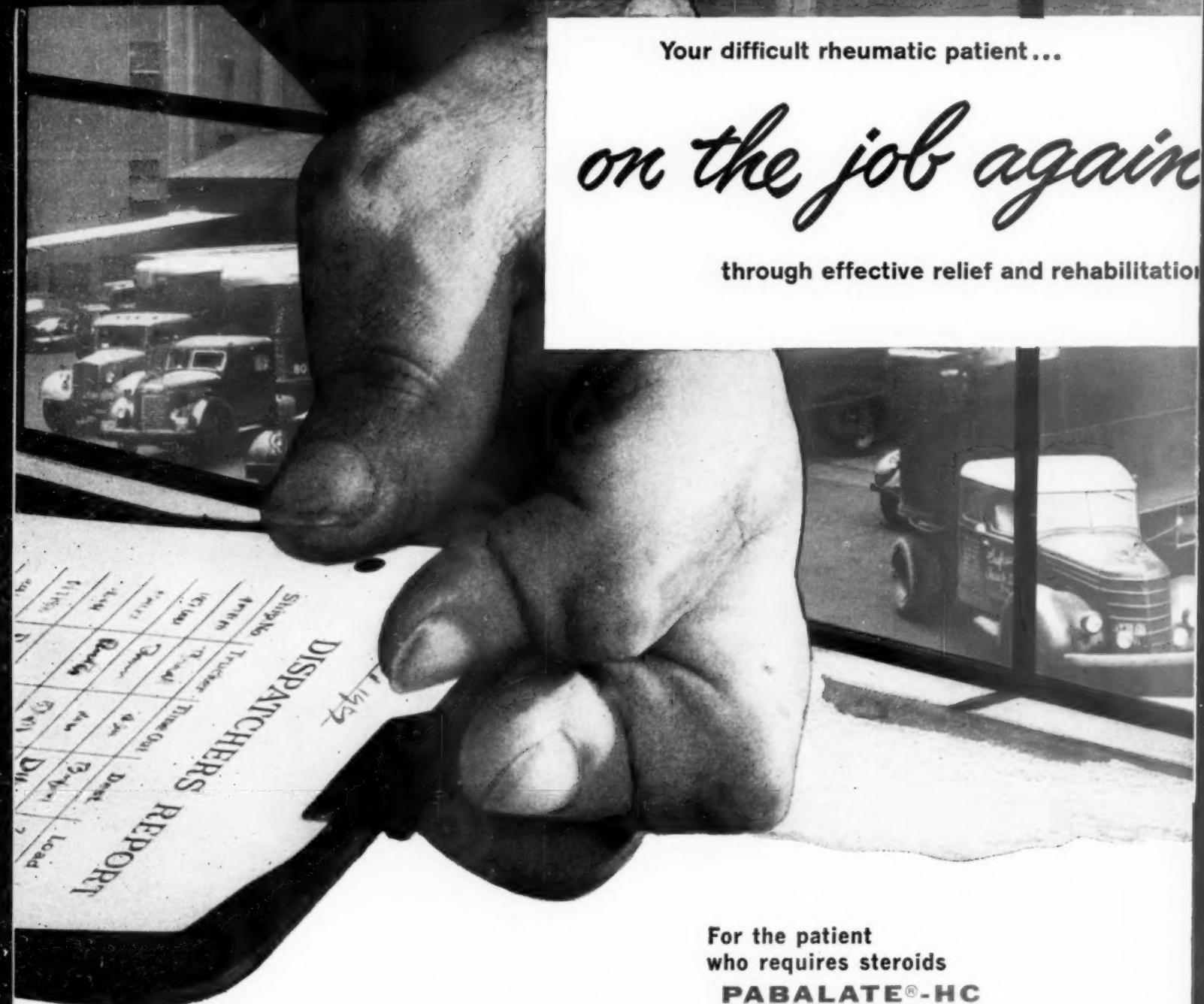
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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

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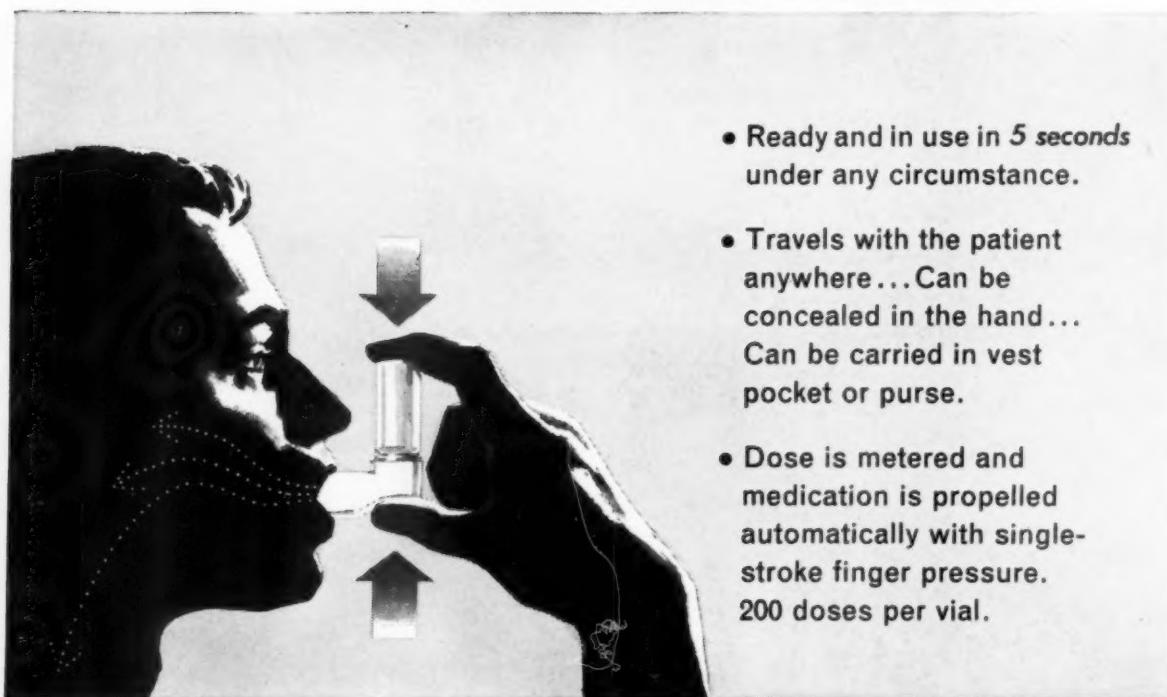
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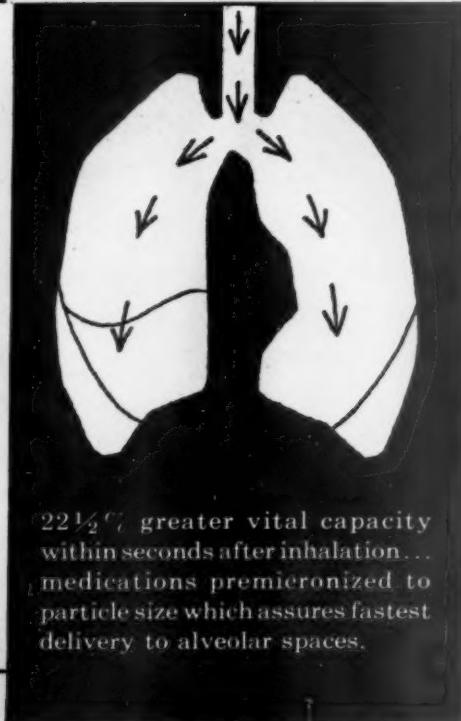
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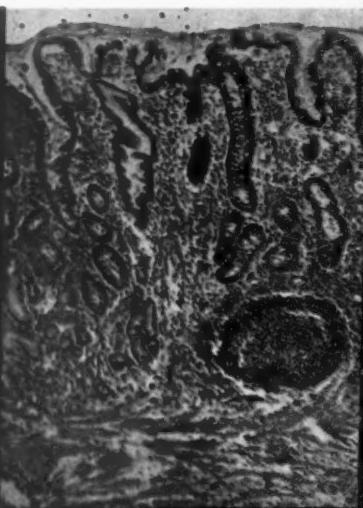
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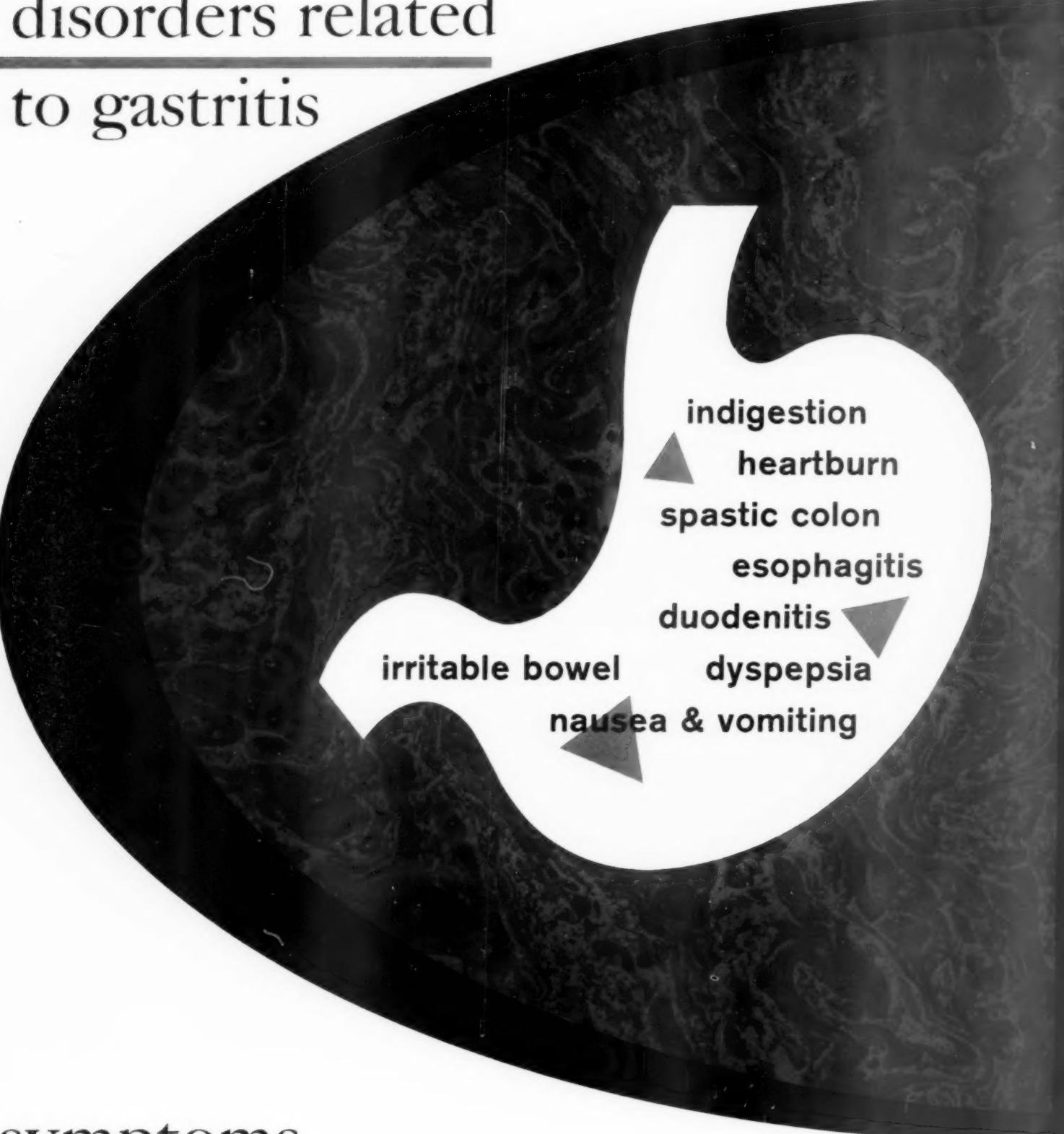


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Irreversible. Considerable distortion of glands. Mucous cells indicate conversion to colonic-type tissue. Fragmentation of muscularis.

Microscopic views of gastric biopsies, courtesy of E. Deutsch, M.D., originally published as part of study, Chronic Gastritis, Deutsch, E., and Christian, H. J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

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Deutsch, E., and Christian, H.J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

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References:

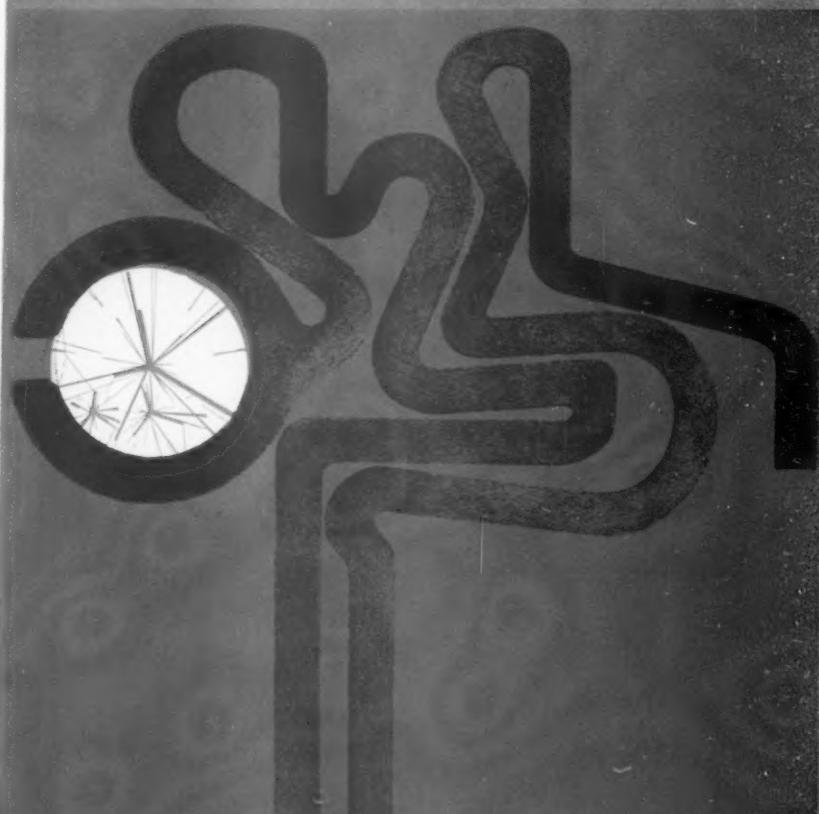
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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

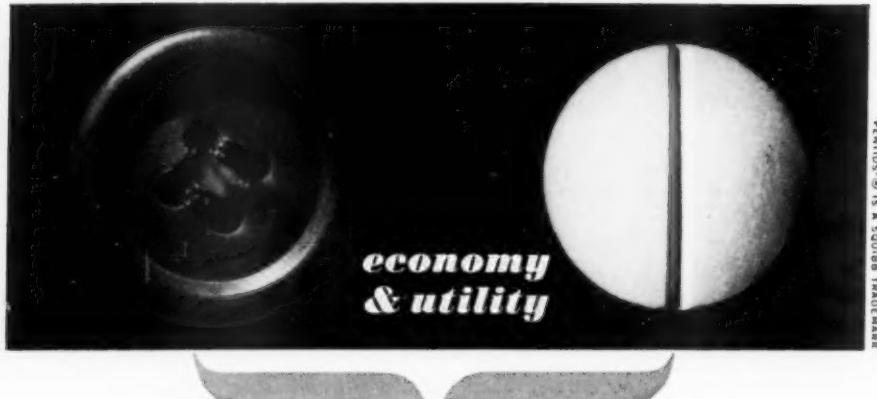
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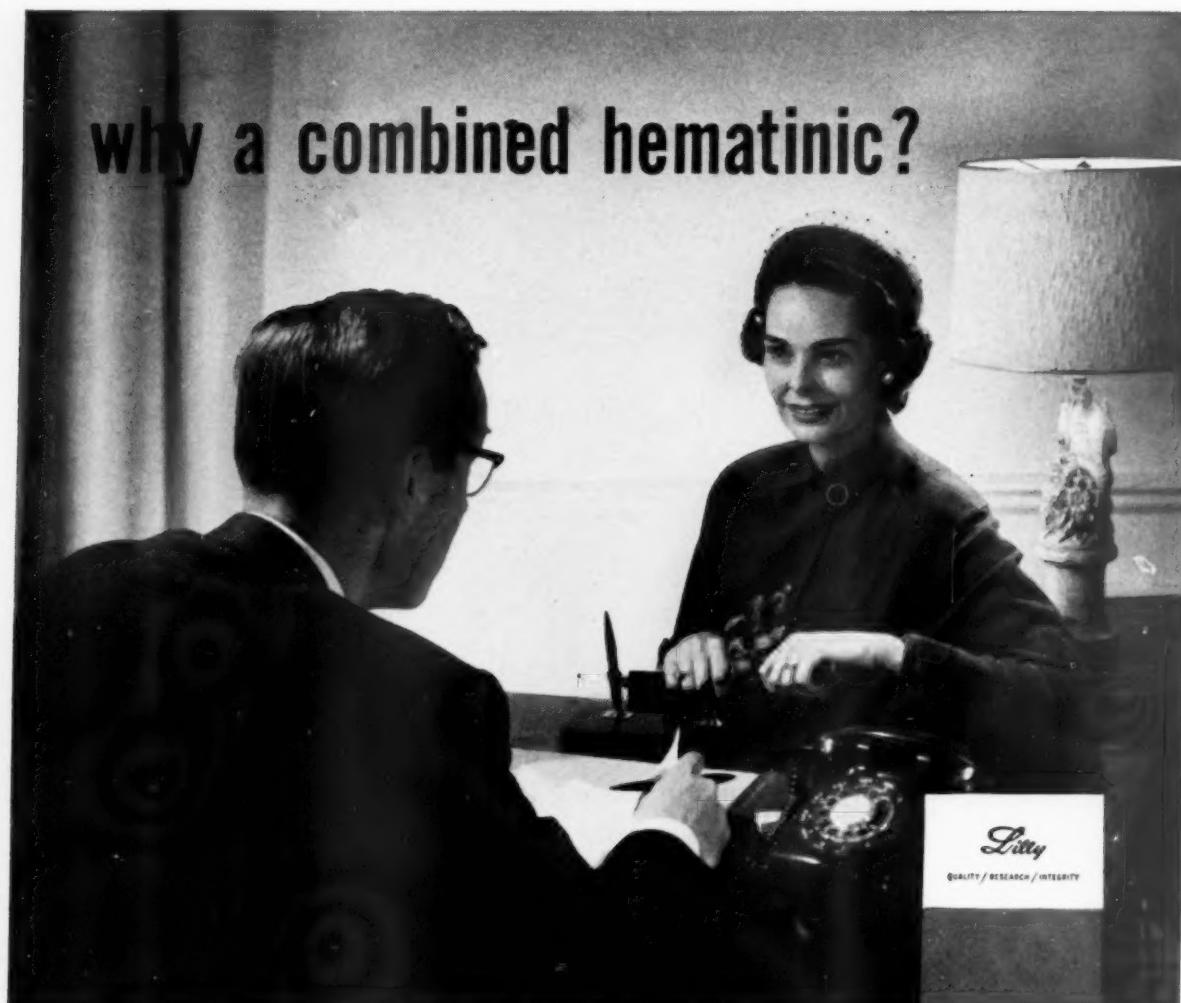
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VOL. XXVIII

APRIL, 1960

No. 4

Editorial

Pyelonephritis—An Enigma

DESPITE the widespread recognition of pyelonephritis as a distinct clinical entity and the availability of an ever-increasing multiplicity of antibiotics, the diagnosis and treatment of the condition remain enigmatic. The disease continues to be a major surprise diagnosis at necropsy [1] and is now perhaps the most common cause of renal disease [2]. As an infection it barely yields quantitative supremacy to infection of the upper respiratory tract [3]. The permanent control of chronic pyelonephritis is said not to exceed 10 per cent [4]. It would seem appropriate for both internist and urologist now to combine their efforts in an attempt to eradicate this potentially fatal disease at the onset [5].

Among those interested in pyelonephritis there appear to be two broad areas of disagreement, the first of which concerns diagnosis. The diagnosis of typical acute pyelonephritis should rarely be missed, provided one recalls that bacilluria and pyuria may be intermittent. Likewise, the diagnosis of typical obstructive pyelonephritis, either recurrent or chronic, ordinarily presents no problem. It is in the delineation of combined infections of the upper and lower urinary tract, when overt symptoms referable to infection of the lower urinary tract distract from the more subtle signs of the infection in the upper urinary tract [6]; in the demonstration of active pyelonephritis when its symptoms are minimal (inapparent active pyelonephritis and pyelonephritis lenta); when the condition complicates other documented forms of renal disease and produces an otherwise unexplainable exacerbation; and when the only overt sign is hypertension, either benign or malignant, that our diagnostic tools are grossly inadequate.

Pyelonephritis may exist without obvious symptoms, without diagnostic alteration in the urine, and despite repeatedly normal urine cultures [7]. Helpful in diagnosis, when present, are persistent pyuria as demonstrated by the Addis technic, the demonstration of pus cell casts, non-specific and therefore non-diagnostic "glitter cells," and possibly the repeated demonstration of a disproportionate fall in the maximal osmolarity of the urine as compared with the glomerular filtration rate [2]. Also, urine cultures after renal biopsy and culture of the specimen obtained at biopsy may help [8]. If all diagnostic efforts have failed and one's suspicion is unallayed, there is little to be said against the oft neglected and possibly old-fashioned test of a therapeutic trial of appropriate drugs.

The second broad area of controversy concerns the importance of bacterial counts and the validity of catheterized versus mid-stream cultures in the female. It is well established that contaminated urine will contain less than 100,000 bacteria per cubic centimeter no matter how it is obtained [4]. As a rough screen to separate contamination from significant bacilluria this may suffice, although it is perhaps not much more helpful than the gram stain of the urinary sediment that should precede all urine cultures since, as a rule of thumb, no organisms will be seen if the bacterial count is less than 10^5 [4]. Bacterial counts cannot be considered truly quantitative, since they rely on bacterial multiplication over an unspecified period of time (the first morning specimen is recommended [4]), and there are many other uncontrollable factors that influence bacterial multiplication, including the inherent vigor of the particular strain involved. However, there is emotional security in numbers, even though,

as is true of so many "tests," errors inherent in the technic may induce a false sense of either security or insecurity. Nor is the bacterial count of value when it is needed most: the patient with chronic pyelonephritis whose abscesses do not at the moment communicate with a nephron and whose urine will be sterile or nearly sterile at the time the culture is obtained. Nevertheless the technic has served to bring the problem of urine cultures into sharper focus and represents a definite contribution to the study of pyelonephritis.

Should mid-stream specimens in the female replace catheterized specimens? The case against the catheter has been boldly championed [9]. This might be construed to imply that the meticulously performed mid-stream method [10] of obtaining urine cultures from females should always be employed. There are plausible reasons for modification of this view. Urine cultures are properly interpreted only by seasoned judgment, a sharp focus on the entire clinical picture, and, above all, recognition of the limitation of culture reports and knowledge of the exact technic used to obtain the culture. Urine obtained through a catheter by uncertain hands or from a buried urethral meatus is not worth culturing. Ideally, the same highly trained personnel, situated in close proximity to the bacteriology laboratory, should obtain all specimens, and the method which produces the safest and most uniform results should be adopted. If rigid standards are met and maintained, for general screening purposes the method of choice would seem to be a mid-stream specimen. Even then, there will always be cases in which a catheterized specimen is preferred, and rightly so.

The basic principles in the management of the patient with pyelonephritis remain unaltered despite the continued introduction of new antibiotics. The search properly continues for eradication of foci of infection. Whenever possible the general health is improved. In the absence of heart failure salt is not restricted, but the protein intake is restricted (0.5 gm./kg.) when azotemia appears.

Although a surgically correctable lesion demonstrable urographically is found in only about one-third of patients with pyelonephritis, it is strongly urged that all patients who have recurrent or chronic pyelonephritis be subjected to the careful examination of a competent urologist before any course of therapy is selected.

The antibiotic treatment of pyelonephritis has two separate goals:

(1) As long as the interstitial tissue of the kidneys is believed to be infected, the dosage of the antibiotic used must be sufficient to raise the plasma level of the drug above its minimal inhibiting concentration; the urinary concentration of the drug should be ignored, because the concentration of antibiotic in most of the interstitial tissue of the kidney is invariably lower than its concentration in the plasma [5,6]. This concept is open to criticism on the ground that the concentration of antibiotic in the interstitial tissue of the kidney must vary with both the integrity of the blood supply and the exact location of the infection in relation to the various parts of the nephron. Moreover, no drug whose antibiotic activity depends on lowering of the urinary pH (mandelic acid, Mandelamine) can have any effect on an infection in the interstitial tissue of the kidney where the pH presumably remains unalterable. Nor can a drug (such as Furadantin) which yields very low blood drug levels in relation to its usual minimal inhibitory concentration of 20 to 30 mg./100 cc. [11] be rationally administered to treat infections of the interstitial tissue of the kidney.

(2) If, on the other hand, the therapeutic goal is to decrease the likelihood of a recurrent ascending infection which might easily infect already damaged and therefore highly vulnerable renal tissue, the antibiotic dosage can justifiably be regulated by the drug concentration in the urine, and under these circumstances the pH of the urine may be considered significant. This is the theoretical basis for prolonged low dosage therapy after presumable eradication of infection in the interstitial tissue of the kidney.

In general, it seems desirable to begin treatment with one of the simpler and safer antibiotics. Combinations of antibiotics may be rationally employed, both for their synergistic effect, when demonstrable *in vitro*, and to delay the appearance of resistant forms [12]. It seems justifiable to reserve the more toxic but also more effective newer bactericidal agents for therapeutic failures or for the desperately ill. Proper selection of the agent or agents to be used depends upon the stage and severity of the disease, reliable help from the bacteriologist, and a nice sense of judgment.

Despite meticulous attention to detail, the treatment of chronic pyelonephritis remains frustrating although it is by no means hopeless.

There are several obvious reasons for this. The normal kidney is relatively immune to infection, but certain forms of renal damage render it highly susceptible to infection and reinfection. In the normal kidney *Escherichia coli* quickly decrease in numbers whereas in an obstructed kidney the rate of growth may enter the logarithmic phase [13]. Obstruction to drainage appears to be the leading common denominator [2], whether the obstruction is due to local changes in the walls of the ureters from infection [14] or, more commonly, to distortion of the renal tubules by scar tissue which creates local areas of stasis in which reinfection easily occurs [15].

An additional cause may well be the indolence of infection, since the majority of agents are most effective when the bacteria are actually multiplying. Interesting but not yet clinically applicable is the suggestion [16] that there may be a primary disturbance in the bactericidal system of the serum of some patients with pyelonephritis. However, no deficiency of gamma globulin has been demonstrated and no excess of competitive non-bactericidal activity was found to account for the primary deficit in pyelonephritis serums with reduced bactericidal power.

It is our present policy to treat the patient with chronic pyelonephritis intensively for the first ten days with the antimicrobial agent or combination of agents that seems most likely to be successful. Considerable reliance is placed on sensitivity tests. Urine cultures obtained during the course of therapy are considered of no value, since the urine and its antibiotic content both are concentrated in the collecting tubules, and the urine hence may be sterile while infection in the interstitial tissue of the kidney is rampant. After ten days, treatment is discontinued and forty-eight hours later another urinary culture is obtained. If still positive, the treatment is re-designed and the patient may be given one of the newer and more toxic bactericidal drugs after the sensitivity of the organism to the drug being employed is determined by the tube dilution technic. When treatment ultimately is successful, long term low dosage therapy is initiated with one of the sulfonamides or one of the antibiotics to which the organism was sensitive in an attempt to prevent recurrent ascending infection or rapid multiplication of organisms in an indolent, relatively avascular area of the kidney until the natural defenses of the body can eradicate the infection. Since

this regimen may encourage the appearance of resistant organisms, it is wise periodically to reculture the urine while treatment is continued and, if the culture is positive, another antibiotic should be given. It is hoped that as intensive prolonged treatment is more widely employed, as newer and safer bactericidal antibiotics appear, and as the underlying mechanism of body resistance is delineated, the final results of therapy will be less disappointing.

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Clinical Studies

Cat Scratch Disease*

A Study of Eighty-Three Cases

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IN recent years many articles have been published about cat scratch disease [1]. Perhaps because of the novelty of the disease most of the reports describe single cases or small groups of cases. In addition, observations on various facets of the disease have been reported, for example: studies of the significance of the skin test [2-4]; the significance of the lymphogranuloma venereum complement fixation test [2,5,6]; and the pathologic features of the lymph nodes [2,7]. The most complete report in the English literature is that of Daniels and MacMurray [8], which describes the clinical and laboratory findings in 160 cases. The purpose of the present article is to present findings in eighty-three cases; forty-six were observed personally.

Cat scratch disease is a more accurate term than cat scratch fever because usually fever is not the chief symptom and some patients have no fever at all. The cardinal feature is a subacute granulomatous lymphadenitis which is sterile when tested with present-day technics for the isolation of fungi, bacteria or viruses. Until more specific tests are devised, it appears wise to require that the reaction to the skin test for cat scratch disease be positive before making the diagnosis. All patients in this series had lymphadenitis and a positive reaction to the skin test.

EPIDEMIOLOGY

The disease is presumed to be due to an infection but so far attempts to isolate an organism have failed. Extensive bacteriological and mycological tests, egg yolk inoculation, mouse brain inoculation and subcutaneous and intraperitoneal injections in guinea pigs have all proved negative. Tissue culture passages have

been made in a variety of cells including Hela, human conjunctival epithelium, monkey kidney and lymph node, adult cat kidney, human embryonic liver and peripheral blood cells, with no evidence of cytopathogenic effect. Until it becomes possible to culture the causative organisms many interesting questions about the disease cannot be answered. Where does the organism exist in cats? Why does the same disease not develop in cats? Why do some patients with a typical illness have a negative reaction to the skin test? Why is the complement fixation test for lymphogranuloma venereum usually negative in children but positive in about half of adult patients? Are there different strains of the organism? Is the causative agent affected by any chemotherapeutic or antibiotic agent *in vitro*?

The role of cats in the transmission of the disease is well established. (Table I.) Although most

TABLE I
CONTACT WITH CATS: COMPARISON IN TWO SERIES
OF CASES

Data	No.	Per cent
<i>Present Series (83 Cases)</i>		
Contact with cats.....	72	87
Cat scratch—57% (41 of 72 cases)		
No contact.....	2	2
No data available.....	9	11
<i>Daniels and MacMurray [8] (160 Cases)</i>		
Contact with cats.....	148	92.5
Cat scratch—58% (93 of 160 cases)		
No contact.....	12	7.5

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of the cats concerned in this series remained healthy, five were sick about the time the patients became ill and two of the five cats died, one with a diagnosis of enteritis.

The seasonal incidence in this series is striking and confirms the observation of Marshall [9] who reported eleven cases from Nova Scotia. In Figure 1 the month of clinical onset of the disease in seventy-eight cases is shown; in five cases the date of onset was not recorded.

The prevalence of the disease in winter is not due to a single epidemic; our cases have been diagnosed over a four-year period. It will be interesting to see whether this seasonal variation is found in other parts of the world. In Canada it is sufficiently noteworthy to be a useful point in diagnosis. Why should the disease be uncommon in summer? Perhaps cats spend so much time roaming outside in the warm weather that the number of times people are scratched decreases significantly during this time of the year.

Our experience supports the general opinion that the disease is of low infectivity. Usually only one member of a family becomes ill, despite the fact that others have had as much contact with the cat and have been scratched by it. In this series there were six instances of multiple infection in the same household.

There is reason to believe that the organism lingers in some households; perhaps cats serve as carriers for prolonged periods. For example, two members of a family had cat scratch disease about the same time and four years later two other members acquired the disease. In another family the mother was affected one year after her daughter had had cat scratch disease. In attempting to establish a diagnosis it is worth asking whether others in the household have had a similar illness recently or in the past.

USUAL CLINICAL FEATURES

In addition to the almost invariable history of contact with a cat, a history of an actual scratch can be elicited in over half the cases. In this regard our series is similar to that of Daniels and MacMurray [8]. In some a primary lesion develops at the site of the scratch. In this series twenty-one patients had primary sores, usually erythematous papules a few millimeters in diameter, which occurred from seven to fifty-six days after the scratch.

The incubation period from the time of the scratch until the onset of the adenitis varied from seven to sixty-one days, usually being seven to

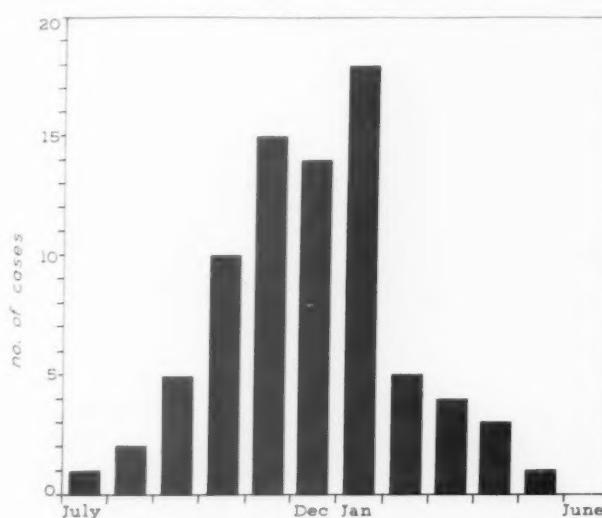


FIG. 1. Prevalence of disease in winter.

fourteen days. One man was scratched repeatedly by his cats; he gave them away, and two months later noted a primary sore on his index finger followed a few days later by inflammation of the epitrochlear and axillary nodes on the same side.

Adenitis was observed in all superficial lymph node areas of the body. The nodes, which were usually tender and ill-defined, occasionally reached a size of 8 to 10 cm. in diameter. Axillary and cervical areas were most often involved, probably because the hands, arms, face and neck are most commonly scratched or brushed against by cats. The frequency of involved sites is shown in Table II.

The axillary nodes alone were involved in thirty-two cases and with other nodes in an additional twelve cases: more than half the patients had inflammation of axillary nodes. Thus there is a good probability that an indolent axillary adenitis is the adenitis of cat scratch disease. To a lesser degree, the same can be said of an indolent inguinal or femoral adenitis. The chief difficulties in differential diagnosis arise with cervical adenitis.

The adenitis progressed to gross suppuration in twenty-six of the eighty-three cases. Suppuration was recognized as early as twelve days and as late as forty days after the onset of the adenitis, the usual interval being three to five weeks. If a non-suppurative adenitis due to cat scratch disease has been present for six weeks, experience would indicate that there is little chance of a frank abscess forming subsequently. Constitutional symptoms are a common but not invariable occurrence. Patients

TABLE II
SITES OF INVOLVED LYMPH NODES

Site Involved	No. of Cases
<i>Single Area Only</i>	
Axillary.....	32
Head and neck.....	17
Inguinal or femoral.....	15
Above scapula.....	1
Epitrochlear.....	1
Site not recorded.....	2
<i>More than One Area</i>	
Axillary and epitrochlear.....	7
Axillary and cervical.....	3
Bilateral inguinal.....	2
Bilateral axillary and bilateral cervical.....	1
Axillary, epitrochlear and pectoral.....	1
Epitrochlear and cervical.....	1

usually complain of fever, malaise, anorexia and fatigue. The fever is generally low grade but, particularly in children or in patients with the rare complication of encephalitis, temperatures as high as 105°F. may be recorded. As a rule the constitutional symptoms last a few days to a few weeks.

UNUSUAL CLINICAL FEATURES

Pain near joints: Occasionally, when the patient consulted his doctor early in the illness, the chief complaint was pain in the region of a joint, aggravated by movement. Five of the patients in this series had a presenting complaint of pain in the region of a joint. Unless the area is palpated to detect enlarged lymph nodes an erroneous diagnosis of arthritis may be made.

Phlebitis of the upper part of the arm accompanied the adenitis in one case.

Paronychias were present in two cases, and may have been the site of inoculation. In both cases the affected nodes were in the axilla.

Erythema nodosum occurred in two patients who had involvement of inguinal or femoral nodes. Others [8,10] have reported erythema nodosum in cases of cat scratch disease.

Multiple sites for adenopathy: Occasionally there were multiple sites for adenopathy (fifteen of eighty-three cases, as indicated in Table II). Sometimes enlarged nodes are found in unusual sites, as others [4,8] have pointed out. One patient in our series had enlargement of a node

located at the upper border of the trapezius muscle.

Splenomegaly was detected in four patients, all children under the age of fifteen.

Encephalitis, the most alarming complication, occurred once in this series. Other cases have been reported [11]. The staff of the Paediatric Service of the New Mount Sinai Hospital, Toronto, has kindly permitted inclusion here of the following case report:

An eleven year old boy went to his doctor because of a mass in the right axilla which had been present for one month. He recalled being scratched on the right wrist by a cat some time before the mass appeared. When first seen his temperature was 100°F.; white blood count was 12,600 per cu. mm., with a normal differential count. A small amount of pus was aspirated from the mass on two occasions. The skin test, using cat scratch antigen, was positive; the complement fixation test for lymphogranuloma venereum was negative. One week later, while watching television, the patient fell off his chair and was described as "jerking all over." He rapidly became semicomatose, restless, and had a temperature of 103°F. The white blood count was 16,800 per cu. mm.; the cerebrospinal fluid was normal. Two days later he was comatose, his eyes diverged and his head was rotated to the right. Kernig's sign was positive and Babinski signs were present bilaterally. A second lumbar puncture revealed 58 lymphocytes per cu. mm. and 56 mg. of protein per 100 ml. During the next few days he improved steadily and made a complete recovery.

ALTERATIONS IN THE BLOOD

The white blood count was usually normal or slightly elevated, the highest level being 16,800 per cu. mm. A few patients had a slight increase in lymphocytes or monocytes. Of interest was an eosinophilia of 7 to 18 per cent in six of fourteen patients with differential white blood counts, the oldest patient with an eosinophilia being twelve years of age. Thus cat scratch disease has a place in the long list of disorders in which eosinophilia may occur [2].

The erythrocyte sedimentation rate was often moderately elevated, the highest figure being 98 mm. per hour (Westergren) in a patient with a large fluctuant abscess. It rarely exceeded 50 mm. per hour, was commonly 20 to 40 mm. per hour, and occasionally was normal.

THE SKIN TEST

The skin test is of considerable help in diagnosis but has a number of limitations. As is well

known, the antigenic material for skin testing can be prepared easily from the pus of patients known to have cat scratch disease. The pus is diluted, one part in four parts of physiological saline solution, and heated for two hours at 60°C. one day and for one hour at 60°C. on the succeeding day. Some authors recommend a dilution of one in five [8], but sometimes a dilution of one in four yields material which evokes stronger skin reactions. The pus is usually of such viscosity that further concentration is impracticable. Not all pus yields a potent antigen; the antigen is present in material obtained from some patients but absent in material from others. We have tested eight lots from different patients but only four were sufficiently potent to be useful.

Each untried lot of skin-testing material must be tested on patients known to have had cat scratch disease. It is useful to perform a skin test with material of established potency at the same time in order that the two reactions may be compared directly. Obviously, in its present form the skin-testing material is not suitable for commercial production.

It is generally accepted that a positive reaction to the skin test consists of an area of induration at least 5 mm. and of erythema at least 10 mm. in diameter forty-eight hours after the injection of 0.1 ml. of material intradermally. Borderline skin reactions are seen occasionally, and repetition of the test may also give equivocal results. Sometimes an equivocal test will be definitely positive seventy-two hours after the injection. Sometimes the result of skin testing is borderline with one material but when antigen from pus of a different source is used the patient has a clear-cut positive reaction [4,8]. It is not uncommon to find a patient who has been scratched by a cat develop a rather indolent adenitis, run the usual course of the disease, and yet have a negative reaction to the cat scratch skin test. Like other writers [8] we have observed that this happens in at least 10 per cent of instances in which the diagnosis has been made on clinical grounds. Perhaps there are different strains of the virus with little or no cross-antigenicity.

A small number of control subjects react positively to the skin test [3,4,8]. We found three positive results in a control group of one hundred nurses and medical students.

Rarely in this series was skin testing accompanied by a brief exacerbation of the disease for a few days. When it does occur the systemic

symptoms may worsen, the nodes may become larger, more tender and painful or, if a sinus is present, the amount of purulent discharge may increase. An exacerbation occurred in three of our patients.

Probably the skin test becomes positive soon after the onset of the illness. One patient had a positive reaction when tested three days after the adenitis was first noticed and two others had positive reactions seven days after the onset. Presumably the skin test remains positive for an indefinite period after recovery: two patients with the usual clinical history had a positive reaction five years later, and another had a positive reaction nine years after the illness.

THE LYMPHOGRANULOMA VENEREUM COMPLEMENT FIXATION TEST

Results of the lymphogranuloma venereum complement fixation test obtained in our cases are compared with those reported by other authors in Table III. Most writers have not accepted dilutions of less than 1:8 as significant. However, we have included the results of Kalter et al. [2] who considered complement fixation at a dilution of 1:5 to be significant. As Armstrong and his associates [6] pointed out, the reaction to the test is much more likely to be positive in adults than in children. Why this should be is not known. The same authors, working in Washington, D. C., found the incidence of positive results in a control series sufficiently high to question the usefulness of the test in the diagnosis of cat scratch disease. In our control group of 120 Toronto adults there were no positive results.

There was a wide range in the intervals between the onset of the disease and the times the reaction to the complement fixation tests were found to be positive. In one case the result of the test was positive as early as one week after the onset of the adenitis, whereas in another case the result was positive five months after the adenitis had begun.

COURSE AND TREATMENT

In our experience the disease had a mild, fairly brief course. Systemic symptoms, when present, usually lasted less than a fortnight and were seldom seriously disabling. The nodes might be painful for several weeks and remain enlarged for a number of months.

Although various antibiotic agents have been

TABLE III
LYMPHOGANULOMA VENEREUM COMPLEMENT FIXATION TEST

Author	Age (yr.)	Subjects	No. Tested	No. Positive at Stated Dilution						Fraction Positive
				1:8	1:16	1:32	1:64	1:124	1:256	
Armstrong et al. [6].....	2-24	Patients	12	0	0	1	0	0	0	..
	37-73	Patients	23	1	1	3	2	0	0	7/23
	Not recorded	Patients	5	0	0	0	0	0	0	0/5
	4-25	Controls	40	1	1	0	0	0	0	2/40
	32-68	Controls	31	2	2	2	0	0	0	6/31
				1:5	1:10	1:20	1:40	1:80	1:160	
Mollaret [5].....	Not stated	Patients	43	0	5	6	3	5	1	1:320
Kalter et al. [2].....	Not stated	Patients	22	5	1	2	2	1	1	0
Spaulding and Hennessy (present series)	2-24	Patients	18	0	1	1	1	0	0	3/18
	26-56	Patients	21	0	1	1	2	3	3	11/21
	18-70	Controls	120	0	0	0	0	0	0	0/120

advocated for cat scratch disease we have been impressed with the failure of any antibiotic drug to shorten the course of the illness. Our patients received various combinations of drugs, including penicillin, sulphonamides, streptomycin, chloramphenicol, tetracycline compounds and erythromycin; none of them had any consistent effect.

If the nodes suppurate one is tempted to treat the abscess by incision and drainage. We have found this to be unnecessary because closed aspiration, repeated every day or two if required, will be effective in nearly all cases. Incision and drainage may result in a sinus which discharges for a long time. Usually closed aspiration prevents the development of a sinus. In only six of the twenty-six cases of gross suppuration in this series was it necessary to aspirate more than once. One patient had seven aspirations, the maximum in the group, a total of 96 ml. of pus being withdrawn. Although Small and Sniffen [12] have advocated excision of the nodes to shorten the course of the illness, we believe that this is rarely necessary. In only one of our cases was the malaise and fever sufficiently prolonged to consider this form of treatment; even in this case the patient felt well six weeks after the onset of symptoms. Removal of inflamed nodes may be difficult because of the periadenitis which is often present.

With the exception of one patient with

encephalitis, none of this group of patients was dangerously ill. The disease itself is not usually a serious one. However, a pathologist may report that an excised node is tuberculous. Chiefly on the basis of biopsy reports four of the patients in this series were told that they had tuberculosis; two were admitted to a sanatorium before cat scratch disease was diagnosed. Pathologists in our area have become wary about making a histological diagnosis of tuberculosis because at certain stages the adenitis of cat scratch disease may be remarkably similar in microscopic appearance. The combination of fever, constitutional symptoms and a persisting enlargement of lymph nodes may lead to a clinical diagnosis of lymphoma; the presence of tenderness of the nodes of course favours cat scratch disease rather than lymphoma.

SUMMARY

The chief points arising from this study of eighty-three cases of cat scratch disease are as follows:

It is a benign infection, endemic not epidemic, with a subacute lymphadenitis as the chief clinical feature. Cats are much the most common vector. The causative organism is probably a virus but so far it has not been isolated. In this series a seasonal incidence is evident, most cases occurring in the period from October to January and almost none in May, June and July. In-

fectivity is low but cases may appear in the same household at intervals of a year or more. Multiple sites of adenopathy, usually neighbouring lymph node areas, are sometimes involved. Certain rather unusual features may be encountered: pain on moving joints, simulating arthritis; phlebitis; erythema nodosum; splenomegaly; encephalitis and eosinophilia.

The skin test has definite limitations but is nonetheless an important confirmatory procedure. In this series the reaction to the lymphogranuloma venereum complement fixation test was usually negative in children but positive in about half of the patients tested who were over twenty-five years of age. When positive, it was a helpful confirmation of the diagnosis.

No antibiotics have been found effective and they need not be given. If gross suppuration occurs, needle aspiration is the best treatment.

The possibility of cat scratch disease should be considered in any patient with a subacute adenitis, particularly if axillary nodes are involved. In suspected cases of tuberculous adenitis, cat scratch disease should also be considered.

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Tuberculous Peritonitis*

A Study of Forty-Seven Proved Cases Encountered by a General Medical Unit in Twenty-Five Years

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TUBERCULOUS peritonitis, which may be present in the absence of clinically apparent tuberculosis elsewhere, is an insidious but treatable disease [1] which often is not sufficiently considered in the differential diagnosis of abdominal disorders. The purpose of this communication is to call attention to its frequency and to review the clinical and laboratory findings that point to its presence. The basis for this study are the records of forty-seven patients proved to have tuberculous peritonitis, encountered on the wards of the Harvard Medical Unit of the Boston City Hospital in the past twenty-five years.

Even when it comes to mind as a diagnostic possibility, tuberculous peritonitis may be exceedingly difficult to prove during life. At times the subtlety of its manifestations may cause it to be overlooked, a fact well known to clinicians both of this and of an earlier generation [2-4]. In the cases reported here there was particular difficulty in recognizing tuberculous peritonitis when it coexisted with cirrhosis and ascites. As Figure 1 and Table I illustrate, tuberculous peritonitis was unsuspected in 55 per cent of patients with cirrhosis, in only 14 per cent of patients without cirrhosis.

TABLE I
THE FALLIBILITY OF DIAGNOSIS IN THIS SERIES OF
PATIENTS WITH TUBERCULOUS PERITONITIS

	No. of Patients	Diagnosed in Life	Suspected but not Proved in Life	Not Suspected in Life
Series as a whole.....	47	22 (48%)	10 (20%)	15 (31%)
Cirrhosis of the alcoholic.....	20	6 (30%)	3 (15%)	11 (55%)
No cirrhosis.....	27	16 (59%)	7 (26%)	4 (15%)

* From the Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

In Osler's era cirrhosis was thought to predispose to peritoneal tuberculosis [5], a complication in as many as 9 per cent of cases [6]. More recently, Ratnoff and Patek in their extensive study of Laennec's cirrhosis in several New York hospitals [7] found the incidence of associated tuberculous peritonitis less than had been reported by previous authors. This was ascribed to "the general decline in the incidence of tuberculosis, particularly abdominal tuberculosis, in the last generation." Indeed, the number of cases of tuberculous peritonitis admitted yearly to a large Massachusetts State Sanatorium has shown a 90 per cent decline between 1926 and 1958 [8]. These data, however, stand in contrast to the experience with tuberculous peritonitis of this medical unit, part of a large municipal hospital. Figure 2 demonstrates that from year to year this unit still encounters as many patients with tuberculous peritonitis as it did twenty-five years ago.

SELECTION OF CASES FOR STUDY

To justify inclusion in this series, the diagnosis must have been established by at least one of the following methods: demonstration of the tubercle bacillus in the ascitic fluid either by guinea pig inoculation or by culture on appropriate medium, or by laparotomy, peritoneoscopy or autopsy. (Table II.)

Twenty-six patients were males, twenty-one were females. The age and sex distribution is shown in Figure 3, in which the black symbols represent patients who also had cirrhosis, of which there were twenty.

Thirty-three of the forty-seven patients died (70 per cent), and autopsy was performed in twenty-seven. Follow-up information is lacking in four patients: two left the hospital at their own request; one was transferred for long-term care to a military hospital, and follow-up is unavailable; another, in 1933, was

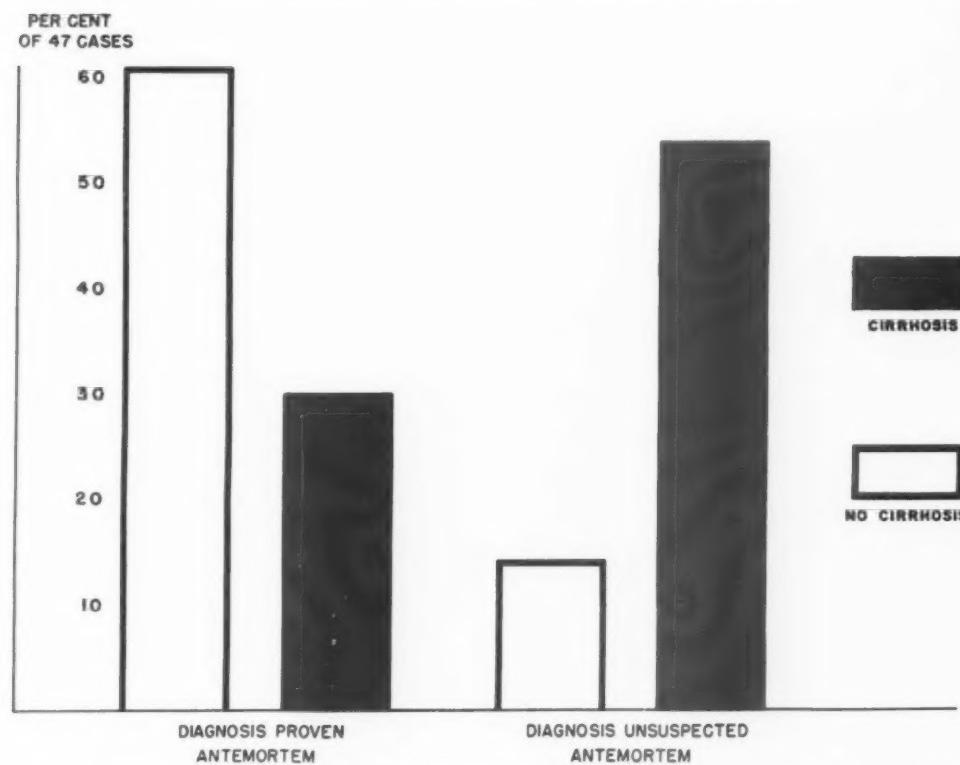


FIG. 1. Frequency with which tuberculous peritonitis was proved and went unsuspected in patients with and without alcoholic cirrhosis.

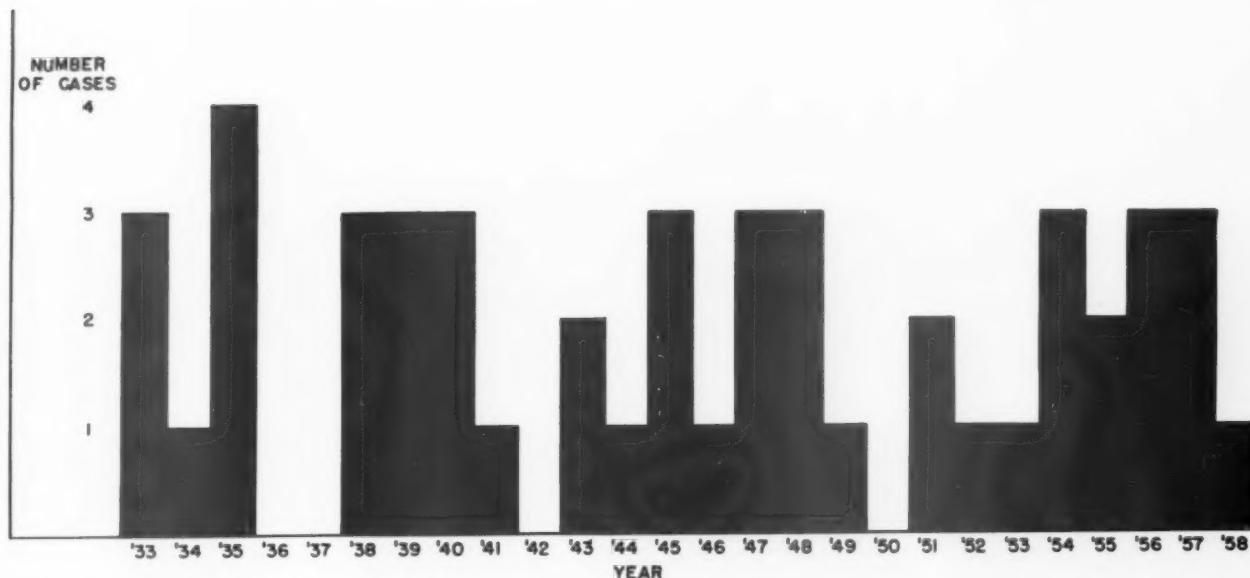


FIG. 2. Yearly experience with tuberculous peritonitis, Harvard Medical Services, Boston City Hospital, Boston.

inadvertently discharged and lost to follow-up before the ascitic fluid was known to be bacteriologically positive.

AUTOPSY FINDINGS

It is not the purpose of this communication to review the pathology of tuberculous peritonitis [3,4,9,10]. In the autopsy patients of this series, the gross ap-

pearance of the peritoneal cavity was described almost uniformly as one in which loops of bowel were interadherent and adherent to the visceral peritoneum and other abdominal organs. In most instances there were multiple small white or gray tubercles covering the surfaces of the viscera; microscopically these were invariably located subserosally. In a few cases there were large caseous abscesses. Twelve of the patients

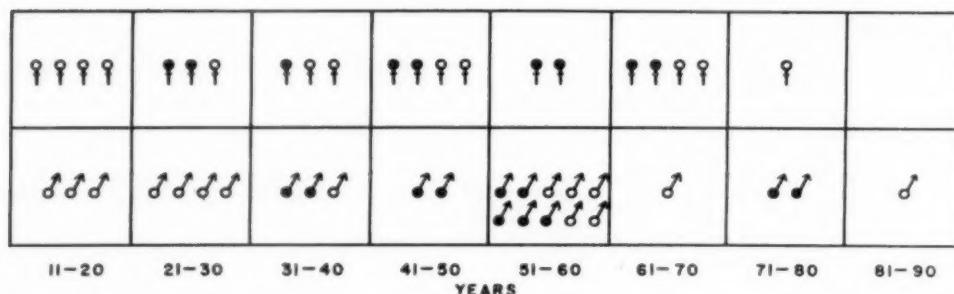


FIG. 3. Age and sex distribution of forty-seven cases of tuberculous peritonitis. Black symbols represent patients with cirrhosis.

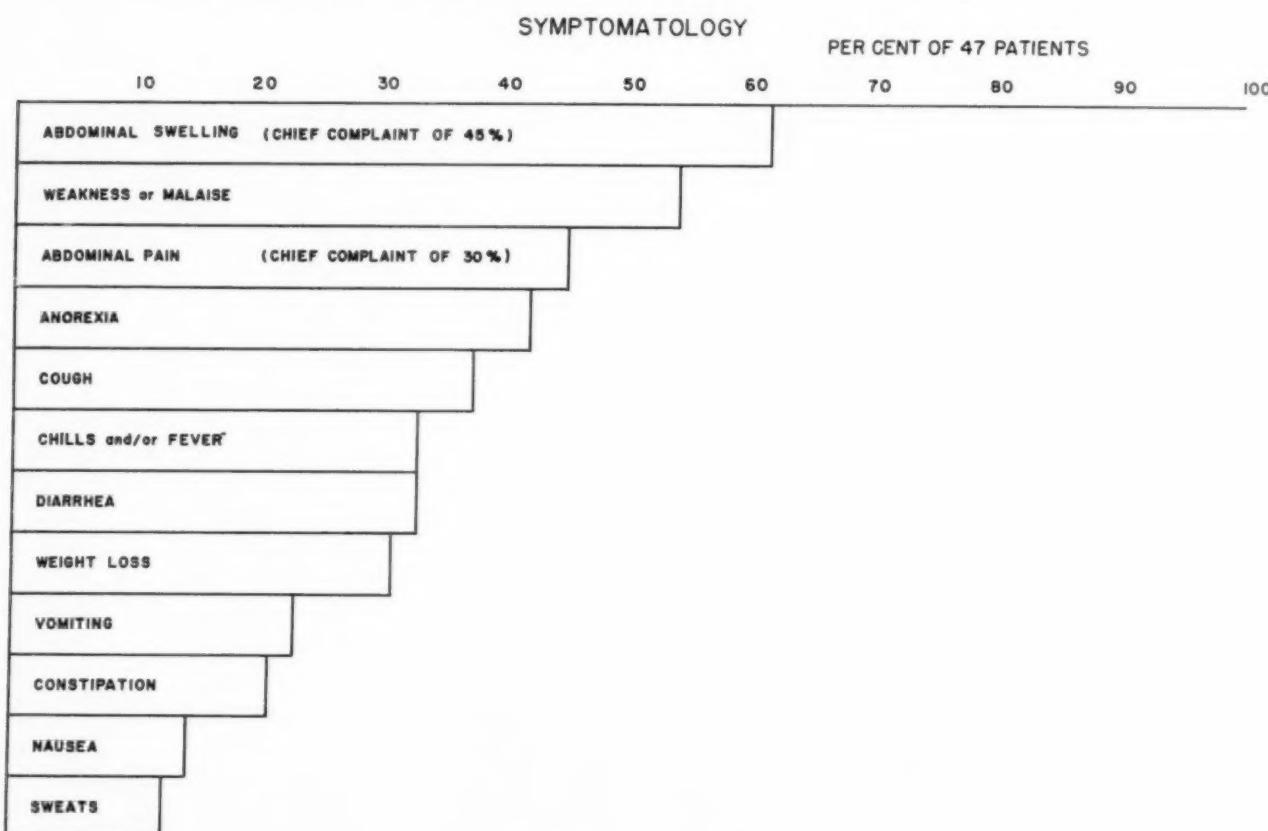


FIG. 4. Symptomatology.

TABLE II
MEANS BY WHICH THE DIAGNOSIS OF TUBERCULOUS PERITONITIS WAS ESTABLISHED IN THIS SERIES

Means	No.
Inoculation of guinea pig with ascitic fluid only	12
Autopsy only	18
Laparotomy only	4
Peritoneoscopy only	1
Culture of tubercle bacillus from ascitic fluid only	1
Two or more of the methods mentioned	11
Total	47

had widespread miliary tuberculosis. Only four patients had tuberculous involvement of the intestinal mucosa, and only one had apparently primary tuberculosis of the genital tract which had secondarily seeded the pelvic peritoneum. For the most part, then, tuberculous peritonitis in this group of patients occurred not by contiguous spread but in all probability was usually hematogenously disseminated.

SYMPTOMS

Twenty-one of the forty-seven patients gave a history of abdominal pain, in fourteen as a chief complaint, with an average duration of ninety-five days and a range from one day to two years. Pain was most often described as cramping, dull or aching, and was located in various parts of the abdomen, often dif-

fusely. Occasionally it was in the right upper quadrant over an enlarged liver. In several instances there was stabbing abdominal pain, similar to pleuritic pain, made worse by coughing, straining or sudden body movements.

Although the complaint of longest duration was abdominal pain, abdominal swelling was a more frequent symptom. It was noted by twenty-nine patients, and in twenty-one it was a chief complaint. In these the average duration was thirty-eight days, with a range from one day to seven months. Figure 4 summarizes the symptoms with which the forty-seven patients presented.

PHYSICAL FINDINGS

All patients at some time during the course of their disease had fever, defined as a persistent elevation or a daily rise above 99°F. in oral temperature. Some patients had afebrile periods of weeks or several months.

In appearance the patients ranged from acutely ill and emaciated to healthy appearing, well developed, and even obese.

Twenty-eight patients (60 per cent) had abnormal physical findings in the lungs. Twenty patients (43 per cent) presented evidence of pleural effusion and/or upper lobe signs strongly suggestive of pulmonary tuberculosis. On examination at the time of admission twenty-eight had a suspicion of free abdominal fluid, and in all but seven manifest ascites eventually developed. The abdomen in only two patients was described as "doughy," although in neither instance was tuberculous peritonitis then initially recorded as a possible diagnosis, presumably because "doughy" abdomens are encountered not uncommonly in elderly patients free of tuberculous peritonitis. The "doughy" abdomen therefore, was an uncommon and unreliable sign of tuberculous peritonitis. In this series the abdomen was characteristically distended with fluid, often drum-like. Three of the twenty patients with cirrhosis and four of the twenty-seven without cirrhosis were free of ascites throughout their illness. Abdominal tenderness was present in twenty-four of the forty-seven patients (51 per cent). In seven the right upper quadrant was tender; in five of these the liver was palpable. Five other patients had tenderness in one or both lower quadrants. Four of these were women, two of whom came to autopsy, and in neither was there evidence of primary tuberculosis of the genital tract. Indeed, in the one autopsy in which the pathologist was of the opinion that tuberculosis originally involving the Fallopian tubes had secondarily spread to involve the peritoneum, the patient never had lower quadrant tenderness. Five patients had epigastric and/or periumbilical tenderness and three had left upper quadrant tenderness, two of the latter over enlarged spleens. Generalized abdominal tenderness was observed in eight patients. Rebound

TABLE III
SALIENT PHYSICAL FINDINGS ON ADMISSION IN
FORTY-SEVEN PATIENTS WITH TUBERCULOUS
PERITONITIS

Finding	Per cent
Fever	100
Râles in upper lobe of lung and/or physical signs of pleural effusion	43
Ascites	60
Abdominal tenderness	51

tenderness was never recorded. Bowel sounds were never found to be absent.

In twenty patients the liver was palpable; eleven were alcoholics and nine were not. On only three occasions was the spleen palpable, twice in patients with cirrhosis.

Four patients had hernias, two inguinal and two ventral. In one patient a draining sinus developed in a paracentesis site, and in another there was a draining sinus at the site of a cholecystectomy scar.

Table III summarizes the salient physical findings on admission.

A PARALLEL ANALYSIS OF SYMPTOMATOLOGY IN CIRRHOSIS WITH ASCITES

In order to test the usefulness of abdominal pain and tenderness, and fever as signs of tuberculous peritonitis when it complicates cirrhosis, we turned to the Mallory Institute of Pathology necropsy records of seventy-five patients with cirrhosis and ascites who did not have peritoneal tuberculosis. All except five had, within the past five years, been patients on this unit at the time of death. Many of these patients did, in fact, have abdominal pain and tenderness and fever, but in most of them postmortem examination disclosed coexisting pathologic conditions which could have accounted for these symptoms. (Table IV.)

Not more than 7 per cent of patients who died with cirrhosis and ascites had abdominal pain that cannot in retrospect be accounted for by one of several associated complications or entities. Of the six whose pain seems not to have had another possible cause, discomfort was located in the right upper quadrant in four, and in three of these was associated with tender hepatomegaly. Abdominal pain was almost never a chief complaint. One is led to conclude that any patient with cirrhosis and ascites who has abdominal pain ought not to be considered

TABLE IV
ASSOCIATED DISEASE FOUND POSTMORTEM IN PATIENTS
WITH CIRRHOSIS AND ASCITES WHO, DURING LIFE,
HAD ONE OR ANOTHER OF THE SYMPTOMS LISTED

Disease	No. of Patients
<i>Abdominal Pain*</i>	
Chronic cholecystitis and cholelithiasis.....	3
Peptic ulcer.....	4
Trauma to abdominal wall.....	1
Thrombosis of superior mesenteric vein.....	1
Hepatoma.....	1
Acute pyelonephritis.....	1
Acute cystitis.....	1
Perforated peptic ulcer.....	1
<i>Abdominal Tenderness†</i>	
Chronic cholecystitis and cholelithiasis.....	1
Peptic ulcer.....	2
Pancreatitis.....	2
Thrombosis of superior mesenteric vein.....	1
Hepatoma.....	1
Tenderness of right upper quadrant over an enlarged liver.....	16
<i>Fever‡</i>	
Gastrointestinal bleeding.....	20
Pneumonia.....	16
Septicemia.....	8
Tuberculosis.....	2
Multiple myocardial staphylococcal abscesses.....	1
Pancreatitis.....	1
Infection of the genitourinary tract.....	3
Staphylococcal enteritis.....	1
Diphtheria.....	1

* In seven other patients, pain was in the right upper quadrant over an enlarged liver in four, and over an enlarged spleen in one. In two others, the pain was described as being "rare and transient" and as "gas pains relieved by food."

† This includes all patients who had abdominal tenderness but one. In this patient, there was no other possible explanation for the tenderness except cirrhosis and ascites alone.

‡ Three patients had a liver which histologically appeared to contain enough necrosis to account for fever [11]. Only one patient had fever for which there was no explanation possible other than cirrhosis.

as having a single uncomplicated disease until proved otherwise. (Table IV.)

Thirty-five per cent of patients with cirrhosis and ascites who died had abdominal tenderness, but in more than half of these the tenderness was in the right upper quadrant over an enlarged

liver, and tenderness located elsewhere could be accounted for by associated pathologic conditions in all instances except one. It may be inferred from this that in the uncomplicated case of cirrhosis with ascites the patient not uncommonly has a tender liver but that tenderness in another part of the abdomen must alert the clinician to the probability of other intra-abdominal disease as well. (Table IV.)

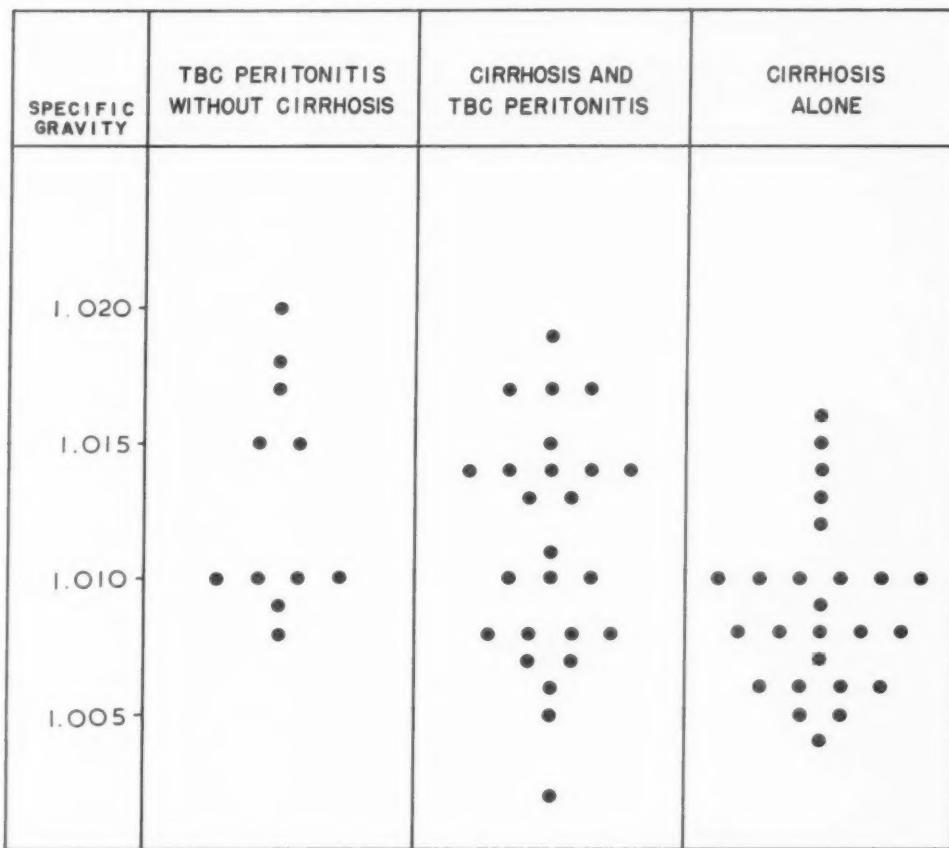
Finally, because it has become customary to believe that the patient with uncomplicated cirrhosis may have a low grade fever, it was surprising and instructive to find that fever, like abdominal pain and tenderness, can only rarely be ascribed to cirrhosis alone. Fifty-seven of the seventy-five autopsy patients with cirrhosis had fever, but in a large number it appeared concomitantly with gastrointestinal bleeding, pneumonia or septicemia. Other infections and pancreatitis accounted for most of the remainder. Three patients were believed to have had enough histological evidence of liver necrosis to account for fever [11], and only one patient had fever with no proved disease except cirrhosis. One may conclude that fever, when it occurs in cirrhosis with ascites, must stimulate a careful search for associated disease. (Table IV.)

ACCESSORY CLINICAL FINDINGS

Hematologic Examination. Five patients with tuberculous peritonitis had initial white cell counts of less than 5,000 per cu. mm. The lowest of these values was 2,100 per cu. mm. and was associated with thrombocytopenia and bleeding phenomena. At autopsy this patient was found to have extensive miliary tuberculous involvement of the bone marrow. Thirty patients had between 5,000 and 8,000 white cells per cu. mm., and of the remaining twelve patients only two had counts greater than 12,500 per cu. mm. (20,800 and 25,700 per cu. mm.). Differential white cell counts were non-contributory as a whole, but in a few instances polymorphonuclear cells constituted as much as 85 per cent of the total. Almost all patients had a moderate normochromic anemia.

Seven patients had consistently positive guaiac tests for occult blood in the stools. Two of four patients with intestinal mucosal involvement fell in this group, but in the others the significance of the blood in the stools went unexplained.

Radiologic Examination. Of the forty-seven cases the charts of forty contained roentgeno-



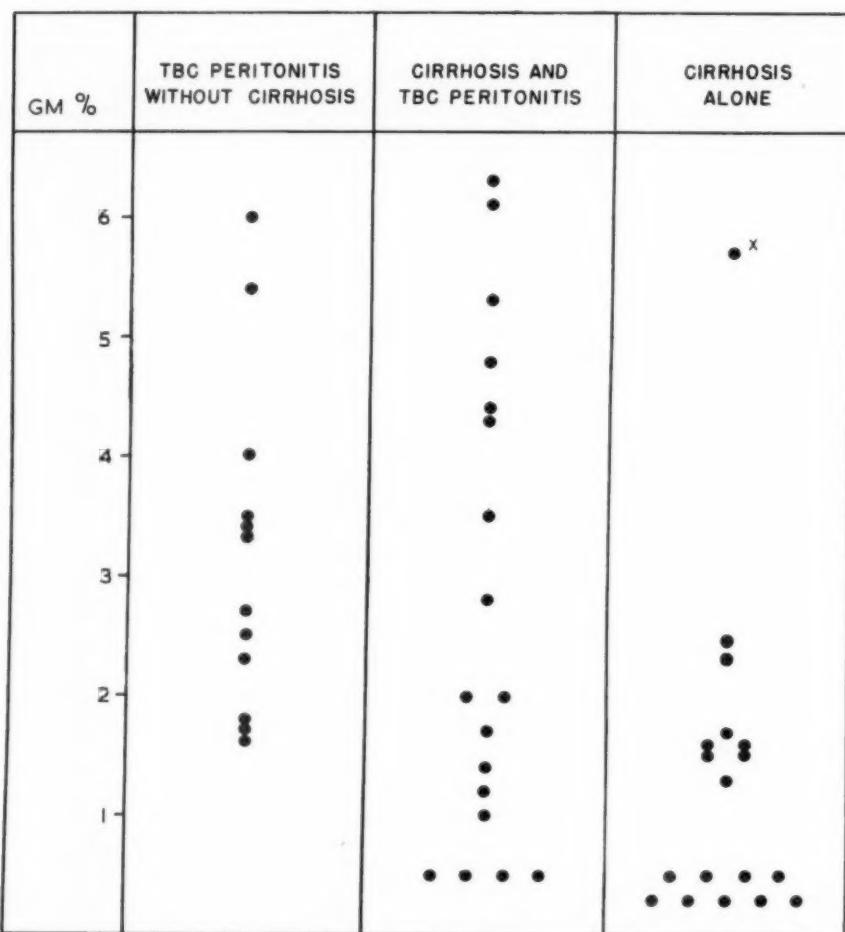


FIG. 6. Ascitic fluid protein concentration.

McPhedran and Peacock described the cell content as "mainly lymphocytes" [14]. We are not aware of published data on patients in whom tuberculous peritonitis was unsuspected during life and diagnosed only at autopsy.

In Figures 5, 6, 7 and 8 are summarized the results of fifty-four separate ascitic fluid examinations made in twenty-eight cases. Specific gravity, protein concentration, total white cell count and differential count are each considered individually. Only two fluids were described as grossly bloody or sanguineous, and one of these was noted to have been obtained from a "bloody tap." Almost all other fluids were described as yellow or amber, cloudy or turbid. Also analyzed are the recorded characteristics of twenty-seven ascitic fluids from twenty-one other patients with cirrhosis of the alcoholic, and ascites. All except five had been patients of this unit within the previous six years, had died and undergone autopsy. All were known not to have had tuberculous peritonitis or other peritoneal

disease. These data are plotted in Figures 5, 6, 7 and 8.

In Figure 5 it is seen that the specific gravity determination of ascitic fluid is of limited value because there is so much spread within each group and so much overlap between them. However, the highest recorded values occurred in uncomplicated tuberculous peritonitis and the lowest values in the patients with coexisting cirrhosis. Among the 468 peritoneal effusions in Paddock's [15] extensive study of serous fluids in disease were included twenty-one "tuberculous fluids," with a reported average specific gravity of 1.020. The range was not reported. Ascitic fluid from patients with cirrhosis ranged in specific gravity from 1.001 to 1.020, with 90 per cent between 1.004 and 1.014 and 95 per cent of values below 1.016. It was surprising to find in our series as well a large number of fluids with specific gravities allegedly much less than 1.010 among the patients who had cirrhosis with and without tuberculous peritonitis. There

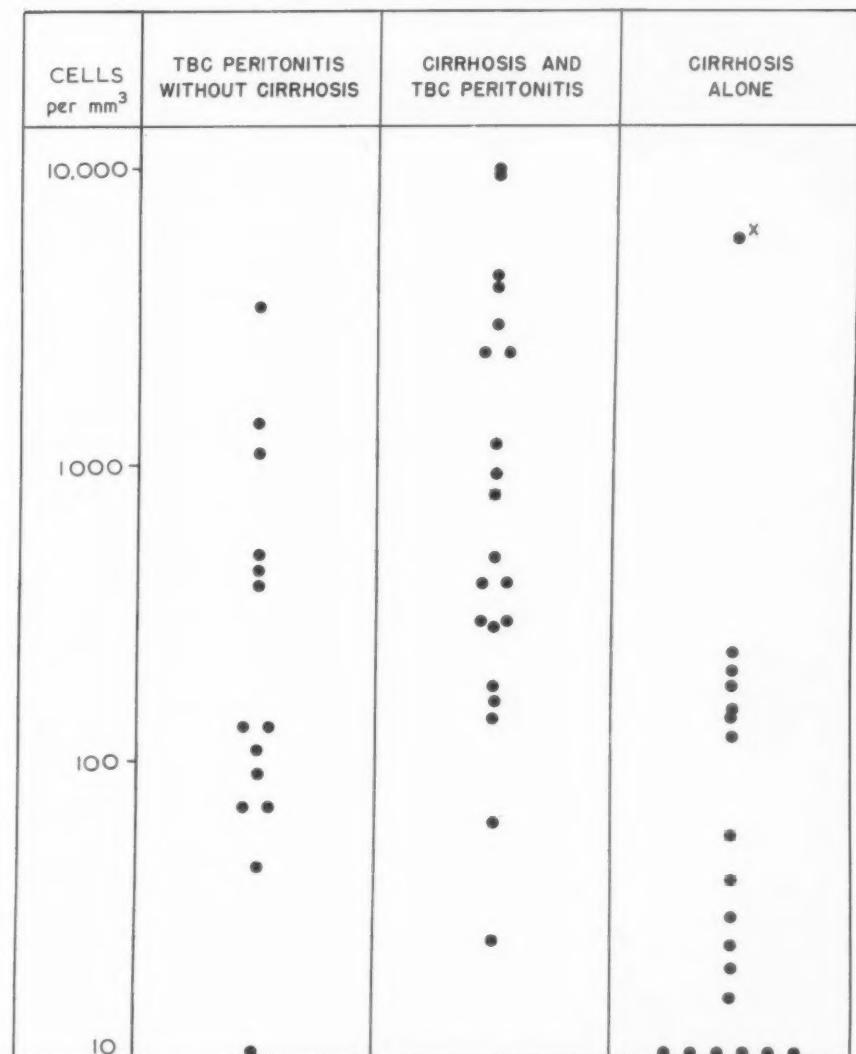


FIG. 7. Ascitic fluid leukocyte count.

is no way to vouchsafe the reliability of any of these individual values, all of which were determined with a hydrometer. Pinner [16], in a study of tuberculous pleural fluid characteristics, demonstrated that when effusion formation occurs in excess of reabsorption, the specific gravity is less than during the later stage in which reabsorption exceeds formation. Even if it is assumed that these general principles apply to ascitic fluid, they do not in any case tell us why a non-chylous, protein-containing ascitic fluid should have a specific gravity less than 1.010. Of course, many patients with cirrhosis and ascites have a low serum osmolarity and in them an ascitic transudate might be expected to have a slightly lower than usual specific gravity, although many of the values recorded in our cases are far too low to be explicable on this account.

Attention has been drawn by Ham [17] to the important effect of temperature on values for specific gravity when determined with an ordinary clinical hydrometer ("urinometer"). It is said that most such instruments now in use have been standardized by their manufacturers to read accurately at 20°C., but some standardized for 15.5°C. and 25°C. are also in general use. In any event, such instruments will record values that are spuriously low when used in fluids warmer than the temperature of standardization. Paddock [15] reported having observed that simple warming of serous fluids from room to body temperature could introduce a variation of as much as 0.010 using a hydrometer standardized for 15.5°C. Using one standardized for 25°C. we have ourselves observed a fall in apparent specific gravity of 0.003—from 1.005 at 25°C. to 1.002 at 37°C. for isotonic saline solution containing 1.0 gm. per cent bovine serum albumin. A hydrometer standardized for 15.5°C. read 0.005 higher at 15.5°C. than at 35°C. This amount of variation with temperature is in substantial agree-

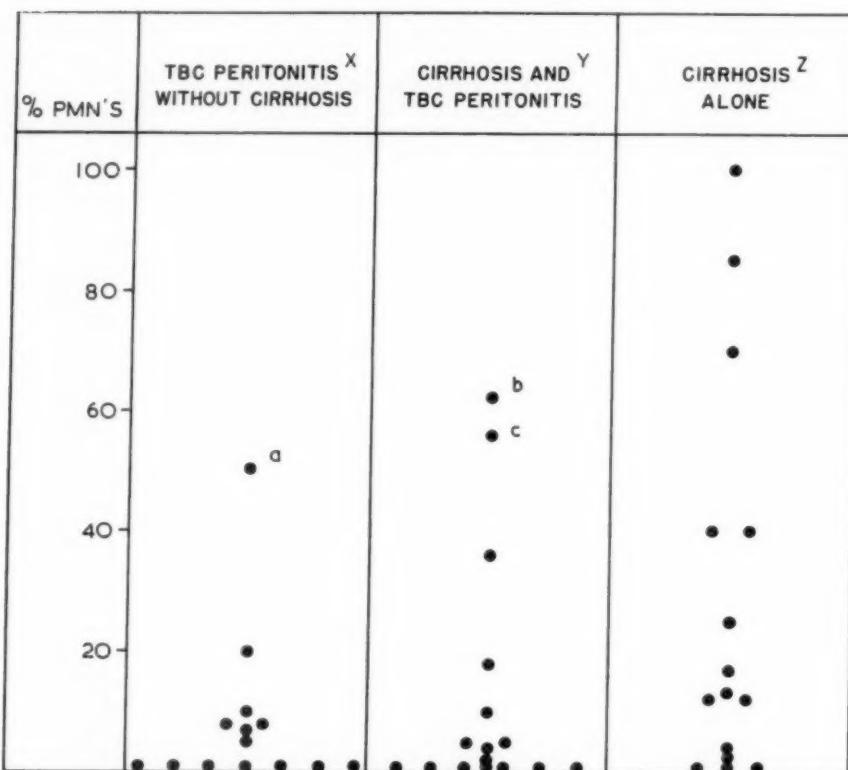


FIG. 8. Ascitic fluid polymorphonuclears per 100 leukocytes. x, one fluid, not recorded here as a point, contained "mostly polymorphonuclears." y, three fluids are not recorded here as points. One contained "90 per cent mononuclears" and two contained "mostly lymphocytes." z, two fluids are not recorded as points. One contained "polymorphonuclears" and the other a "rare polymorphonuclear." a, on another occasion fluid from the same patient contained no polymorphonuclears. b, on two other occasions fluid from the same patient contained 36 per cent and 6 per cent polymorphonuclears. c, house officer reported that he was not certain that these were polymorphonuclears.

ment with the published correction value, viz. 0.001 for each 3°C . above the standardization temperature of the hydrometer [17].

It is not possible to determine now the specifications of the hydrometers that have been used on this medical unit during the past twenty-five years (although currently in use are ones standardized for 15.5°c.), but it has been the practice of its house physicians to "work up" body fluids as soon as possible after they have been drawn and often are still warm. When it is also borne in mind that the error in reading the hydrometer scale may be ± 0.002 , the several low values shown in Figure 5 become less difficult to interpret. In this connection we were recently directed to a patient who had cirrhosis with a marked serum hyponatremia and whose ascitic fluid had been reported by the house physician to have a specific gravity of 1.003. By gravimetric determination at a fluid temperature of 20°c., the specific gravity was found to be 1.008.

One is justified in concluding that published values for serous fluid specific gravity should be viewed with caution when unaccompanied by facts regarding

temperature and hydrometer specifications, especially when it is often the practice to oversimplify and use (with diagnostic implications) a single value as a sharp line by which to classify separately "transudates" and "exudates."

Figure 6 shows protein concentrations in the three categories. With one exception, patients with uncomplicated cirrhosis had ascitic fluid protein concentrations of less than 2.5 gm. per cent. The exception was a woman who, although she had no grossly apparent associated intra-abdominal disease, did have a proved staphylococcal septicemia. Whether there were, in fact, patches of peritonitis that were overlooked at postmortem examination, or whether the septicemia had in some way injured the capillary endothelium causing excessive loss of protein into the abdominal cavity, are matters for speculation. Although a significant number of patients with tuberculous peritonitis in both the

group with cirrhosis and the group without cirrhosis also had protein concentrations of less than 2.5 gm. per cent, the majority of the values fell above this level. Again, applying to peritoneal effusions what is known about pleural effusions [16], protein concentration, like specific gravity, is a function of the relative importance of formation versus reabsorption, lower when the former and higher when the latter predominates. From a practical standpoint it can be concluded that although a low ascitic fluid protein concentration fails to rule out tuberculous peritonitis, a concentration greater than 2.5 gm. per cent in cirrhosis makes it imperative to search for associated intra-abdominal disease (not necessarily tuberculous peritonitis).

Figure 7 illustrates the fact that the total white cell count of ascitic fluid from patients with uncomplicated cirrhosis was, with only one exception, less than 250 per cu. mm. The exception is the patient with staphylococcal septicemia already mentioned. Patients with tuberculous peritonitis often had counts in this same low range also, although somewhat more than half had higher counts ranging up to 10,000 per cu. mm. From this it is clear that the patient who has cirrhosis with ascites and whose ascitic fluid contains more than 250 white cells per cu. mm. must be considered to have associated intra-abdominal disease (not necessarily tuberculous peritonitis); a count less than this does not ensure the absence of tuberculous peritonitis.

In Figure 8 is charted, as an index of the differential count, the per cent of polymorphonuclear leukocytes in the total ascitic fluid leukocyte count. This is preferable to charting the percentage of lymphocytes because the one type of cell about which there was apparently the least confusion in identification was the polymorphonuclear. When the concentration of this cell is low, there must be a high concentration of mononuclear cells of all kinds. In a few instances no numerical data were cited; there were only statements such as "mostly lymphs" or just "polys." Where there were "mostly lymphs" there must have been few polymorphonuclear leukocytes. It would appear that patients with uncomplicated cirrhosis, like patients with tuberculous peritonitis (whether or not they have cirrhosis), tend to have fewer polymorphonuclear than mononuclear cells in the ascitic fluid. A few, on the other hand, had high polymorphonuclear counts. By way of con-

trast, thirteen of thirty-four tuberculous fluids contained no polymorphonuclear leukocytes at all, and in no case could it be clearly established that ascitic fluid from any single tuberculous patient contained more than 20 per cent polymorphonuclear leukocytes. It is unfortunate that no careful distinction was drawn between small and large lymphocytes because there is a strong impression on the part of some [18] that the finding of an ascitic fluid with nearly all small lymphocytes is in most cases diagnostic of tuberculous peritonitis. It is not possible to confirm this impression with the available data, but it is possible to state that such a picture is not a necessary part of the diagnosis. A recently published monograph [19] on cytology of serous effusions cites three cases, two in which there was "a considerable lymphocytic predominance" and a third in which "neutrophils and lymphocytes occurred in approximately equal numbers." Until more data are available, one may tentatively conclude that an ascitic fluid which is consistently shown to contain more than 20 per cent of polymorphonuclear cells is not likely to indicate tuberculous peritonitis.

One of the disturbing pitfalls in the diagnosis of tuberculous peritonitis is the fact that repeated bacteriological examination of the ascitic fluid may be negative, a circumstance well known to previous authors [3,4]. In this series the correct diagnosis was never unequivocally established by visual identification of acid-fast organisms in smears of the ascitic fluid, despite twenty individual attempts to do so. Thirty-three guinea pigs were inoculated with separate ascitic fluid specimens from twenty-one patients. In four cases the pig died prematurely of non-tuberculous bacterial infection. Eight fluids, representing seven patients, were reported as negative for tuberculosis. Thus, of the guinea pigs who survived inoculation long enough for the disease to develop, it failed to do so in 28 per cent. This is not surprising in view of the generally recognized fact that the tubercle bacillus can be demonstrated in less than half the cases of tuberculous pleural effusion.

The experience with *Mycobacterium tuberculosis* culture in test tube medium was even more disappointing. Of twenty cultures 60 per cent were reported negative. Nevertheless, in four instances a culture was positive when the response in the guinea pig was negative, and five times the culture was negative when the response in the guinea pig was positive. It

therefore appears desirable to continue to use both methods for detection.

These data amply demonstrate that tuberculous peritonitis may well be present in a distended abdomen which yields fluid that is physically, chemically, microscopically and bacteriologically within normal limits. It would seem that the widespread practice of labelling such fluids "benign" is unjustified and may lead to a dangerously false sense of security.

REPRESENTATIVE CASE REPORTS

The following cases were chosen for presentation because among them they illustrate many of the pitfalls encountered in the recognition of tuberculous peritonitis.

CASE I. A forty-four year old obese, mildly diabetic woman was first admitted to the hospital because of epigastric pain and gaseousness of three months' duration. Gastrointestinal series revealed an ulcer on the lesser curvature for which she underwent gastrectomy. At surgery a single gallstone was palpated, but exploration revealed no other abnormality.

During the ensuing year she had a cholecystectomy and was hospitalized on three occasions for "post-gastrectomy syndrome," hepatic decompensation attributed to "cirrhosis" and draining abdominal sinuses (not examined for acid-fast bacilli). She persistently denied any alcoholic intake. A liver biopsy specimen revealed "non-specific fibrosis."

Over the following six months four paracenteses revealed specific gravities in the range 1.008 to 1.010; one cell count was 420 white blood cells per cu. mm., all "monocytes and epithelial cells"; another time it was 90 white blood cells per cu. mm. with 60 per cent "monocytes" and 40 per cent "lymphocytes." The total protein ranged from 1.8 to 2.4 gm. per cent. One injected guinea pig "died in twenty-four days . . . no diagnosis," one "died in two weeks," one was negative, and one still unreported at the time of her final admission. Her chest roentgenograms remained within normal limits. She had a persistent low grade fever, and her recurrent ascites and peripheral edema responded intermittently to the administration of diuretics and salt restriction. Although for months she complained bitterly of generalized abdominal pain and tenderness, the bowel sounds remained normal. A psychiatric consultant diagnosed mid-life depression with "grief and guilt reaction" over her husband's death one and a half years before, leading to complete anorexia and starvation.

On her last admission (eighteen months after her first), a guinea pig inoculated more than six weeks before was reported positive for tuberculosis. She was transferred to a sanitorium for the care of extra-pulmonary tuberculosis where, despite the insti-

tution of specific therapy, she died. No autopsy was performed.

Neither persistent abdominal pain nor development of postoperative fistulous tracts in an abdominal wound nor severe recurrent ascites sufficed in this instance to raise a suspicion of tuberculous peritonitis. In the absence of fever or a strikingly abnormal ascitic fluid, and in the face of repeated failure of ascitic fluid inoculations to infect a guinea pig, the proper diagnosis was made too late. The normal chest roentgenograms and minimal amount of fever for many months were probably thought to make tuberculous peritonitis a highly unlikely diagnosis. It is of interest that the ascitic accumulation was retarded or diminished somewhat by bed rest, and the administration of a low salt diet and mercurial diuretics.

CASE II. A thirty-one year old woman was admitted because she had had a fever for ten days. No cause was found. The fever, which was unaccompanied by any other symptoms of note, disappeared. She remained well until sixteen months later when daily spiking fever recurred, with three weeks of gradual abdominal swelling and diarrhea. There was leukopenia, and a roentgenogram of the gallbladder suggested the presence of a non-opaque stone. Bone marrow culture was negative for tuberculosis. A barium enema was read as suggestive of ulcerative colitis, and for a time this was entertained as the cause of the fever until *Salmonella newington* was grown from a stool specimen. Serious consideration was being given to a therapeutic cholecystectomy on the assumption that the gallbladder was the nidus of chronic infection with salmonella when a mass was discovered in the right lower quadrant which was tender and which was thought possibly to represent a perforated regional ileitis although tuberculosis was also considered. At surgical exploration the peritoneum was studded with tubercles. Although ascitic fluid removed by subsequent paracentesis was reported as positive in the guinea pig, the fluid removed at the time of surgery was negative. The patient was treated with antituberculous chemotherapy with apparent cure.

In this patient, disseminated tuberculosis finally manifested itself as peritonitis with ascites. It was diagnosed by exploratory laparotomy which was astutely undertaken in the presence of two "red herrings."

CASE III. An eighty-seven year old Japanese man was admitted because of leg, abdominal and scrotal swelling of three weeks' duration. Ascitic fluid was sent

for acid-fast culture and guinea pig inoculation, but no report was received before discharge. He was assumed to be in heart failure because, although there was no clinically apparent elevated venous pressure, there was a 25 pound weight loss while receiving digitalis and mercurial diuretics. There was a short-lived bout of fever with a temperature of 102°F., no cause for which was evident, and a chest film revealed no abnormalities. He was readmitted little more than a month later—emaciated and cyanotic, with clubbed fingers. Although the venous pressure was normal, heart failure was still assumed to be the likely cause of the ascites and peripheral edema because of the apparent weight loss following administration of digitalis and diuretics on the previous admission. Metastatic malignancy and cirrhosis of unknown etiology were also mentioned as possible diagnoses. An interpreter was told that the patient had never indulged in alcohol. He died on the sixth day before receipt of a report from the laboratory to the effect that an ascitic fluid mycobacterial culture planted at the time of the previous admission was found to be positive.

Metastatic malignancy, cirrhosis and heart failure came to mind as possible causes of ascites, but even though there was never any clinical evidence of an elevated venous pressure, the latter was nonetheless assumed to be its etiology because the distention diminished after treatment with digitalis and diuretics. Ascitic fluid was inoculated into mycobacterial culture medium as a part of the "routine" workup but the patient died before the correct diagnosis was evident.

CASE IV. A sixty-five year old chronic alcoholic woman was admitted because of abdominal pain and fever. She had had the beginning of abdominal pain and swelling one and a half years before, at which time a liver biopsy specimen demonstrated cirrhosis with fatty infiltration. For a year before admission her appetite had been poor, and a doctor prescribed maintenance prednisone as a "tonic." Two months before admission she began to have fever daily. She was obese, jaundiced, and had all the usual stigmas of cirrhosis. A white patch was seen in one fundus oculi. No tenderness was noted on abdominal examination. She was assumed to have cirrhosis of the alcoholic, with ascites and impending coma. The total white blood cell count was more than 20,000 per cu. mm. with a lymphopenia. The ascitic fluid contained 180 white blood cells per cu. mm., 90 per cent of which were lymphocytes. Because of the persistent fever, miliary tuberculosis was considered. An OT test was positive at 1:10,000, but no evidence of active tuberculosis was uncovered. After six weeks she was transferred to a chronic disease hospital. The diag-

noses at discharge were Laennec's cirrhosis and "fever of unknown origin probably due to liver necrosis." She died at the chronic disease hospital within less than a month, and at autopsy was shown to have tuberculous peritonitis as well as Laennec's cirrhosis. It was only after her death that tuberculosis was found to have developed in the guinea pig which had been inoculated with ascitic fluid at the time of her last admission to Boston City Hospital.

Abdominal pain as a chief complaint in a patient with cirrhosis of the alcoholic, who had been receiving cortisone, had a whitish fundal exudate, persistent fever, and chiefly lymphocytes in the ascitic fluid, should have suggested the possibility of coexisting tuberculous peritonitis.

CASE V. A fifty-four year old woman, a chronic alcoholic, was admitted because she had had ascites for two months and pain in the left upper quadrant. She had spider angiomas with tense ascites and a prominent venous pattern over the abdomen. Liver functions were markedly deranged. The ascitic fluid contained 25 white cells per cu. mm., all lymphocytes, and its specific gravity was 1.008. Chest film showed "peri-bronchial infiltration." The possibility of miliary tuberculosis was considered strongly because of daily fever with temperatures between 100° and 100.4°F. Gastric aspiration, bronchial aspiration and two bone marrow specimens were negative for tuberculosis by guinea pig inoculation; a biopsy specimen of a scalene node was histologically within normal limits. The ascitic fluid was negative both in the guinea pig and in special culture medium. The discharge diagnosis was Laennec's cirrhosis with ascites. She was readmitted three and a half years later with marked recurrent ascites, all the usual stigmas of cirrhosis, hyponatremia and remitting and exacerbating coma. She was considered to have typical cirrhosis and was transferred to a metabolic ward for the study of ascites formation. During much of her course, but not all of it, she had a daily oral fever with spikes in temperature to about 100° and at times 101°F. The possibility of tuberculous peritonitis was raised several times but was considered unlikely because a single ascitic fluid inoculation into a guinea pig was negative. She died eight months after admission. Post-mortem examination disclosed tuberculous peritonitis and acute tuberculous pneumonia as well as fatty nutritional cirrhosis. Only after death was an ascitic fluid taken six weeks before death found to have been positive for tuberculosis in the guinea pig.

Miliary tuberculosis as a coexisting disease was given serious consideration but despite numerous tests this diagnosis could not be established and cirrhosis was assumed, therefore, to account for

the entire clinical picture. The ascitic fluid became bacteriologically test-positive too late to be of use. In retrospect, persistent fever and prominent abdominal pain were the clues to the presence of tuberculous peritonitis.

CASE VI. A forty-one year old Negro man who had been a chronic alcoholic for many years had had a previous admission for gastritis and hematemesis. On admission he was severely jaundiced, with markedly deranged chemical findings indicative of liver disease and a slightly distended abdomen without obvious fluid. His course was puzzling because although his jaundice cleared over a period of several weeks he ran a daily spiking fever with a temperature as high as 104°F. on occasion, although the chest roentgenogram did not show any abnormalities, and blood and urine cultures remained negative. Gross hematuria developed. Ascites became evident three months after admission, and the ascitic fluid was found to contain a predominantly mononuclear exudate. He became extremely weak and cachectic. Miliary tuberculosis with tuberculous peritonitis was considered highly possible and an exploratory laparotomy was performed. Omental tissue contained granulomas, although the open liver biopsy revealed no tubercles. It was only later that the ascitic fluid was reported to be positive for tuberculosis in the guinea pig, but in the meantime triple anti-tuberculous therapy had been instituted. Over a period of several weeks he began to feel stronger and the temperature approached normal. He was then transferred to a tuberculosis sanatorium. At least three sputums, several gastric fluids and twenty-four-hour urine collections were negative in the guinea pig.

This instance of abdominal tuberculosis in a patient with cirrhosis illustrates the difficulty of diagnosis. Exploratory laparotomy established the correct diagnosis and resulted in prompt treatment.

CASE VII. A fifty year old chronic alcoholic had noted abdominal swelling for six weeks. On examination he had all the stigmas of cirrhosis, and soon after admission delirium tremens developed. He was slightly jaundiced. Because he was believed to have typical cirrhosis, he was transferred to a metabolic ward for detailed studies of "ascites and protein metabolism." While on the metabolic ward he had recurrent massive ascites and was tapped many times. He died delirious, disoriented, in pulmonary edema, seven and a half months after admission. The final clinical diagnoses were cirrhosis and pulmonary edema. At postmortem examination the peritoneal cavity was full of fluid in which there floated specks of fibrin; the intestinal serosa was dull grey and covered with fibrin; loops of intestine were interadherent; and

the omentum, greater mesentery and parietal peritoneum were all studded with tubercles. The immediate cause of death was bronchopneumonia. He had cirrhosis, a few tubercles in the lung, under the splenic capsule, in the intestinal wall under the serosa, in the peripancreatic fat, and in the liver.

SUMMARY AND CONCLUSIONS

1. Tuberculous peritonitis has been encountered at least forty-seven times by a medical unit of a municipal hospital, and with unabating frequency during the past twenty-five years. It was likely to go unsuspected, especially in patients who also had cirrhosis.

2. Study of the symptomatology and physical findings demonstrated that abdominal pain, fever, or abdominal tenderness elsewhere than in the right upper quadrant in a patient who has cirrhosis with ascites should serve to raise the suspicion of coexisting disease, of which tuberculous peritonitis is one possibility.

The "doughy abdomen" was found to be a rare and unreliable sign of tuberculous peritonitis. On the contrary, distention of the abdomen with obvious ascites was characteristically present.

The absence of physical or radiologic evidence of pulmonary tuberculosis was by no means inconsistent with the diagnosis of peritoneal tuberculosis.

3. The ascitic fluid is often physically, chemically and bacteriologically within normal limits, but when there are more than 2.5 gm. per cent total protein or more than 250 leukocytes per cu. mm. one should consider tuberculous peritonitis a distinct possibility, particularly when the per cent of polymorphonuclear cells is low. The persistent finding of more than 30 per cent polymorphonuclear leukocytes makes tuberculous peritonitis an unlikely diagnosis.

Nearly one of every three ascitic fluid inoculations into guinea pigs was negative for tuberculosis, and more than half of the attempted mycobacterial cultures were negative. Because either was sometimes positive when the other was negative, there is reason to do both when the disease is suspected.

4. In some cases exploratory laparotomy was the only means by which it was possible to establish a proper diagnosis within a reasonable time.

5. The two most common reasons for missed diagnoses were (1) not considering its likelihood because the ascitic fluid was "benign" and

(2) attributing whole clinical pictures to single diagnoses.

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An Experimental Malabsorption Syndrome Induced by Neomycin*

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PREVIOUS reports from this laboratory [1,2] have implicated neomycin as the etiologic agent in the production of a fecal excretory pattern resembling that which is commonly observed in idiopathic steatorrhea. In these studies large doses of neomycin given orally resulted in increased fecal excretion of total fat, free fatty acids, soaps, nitrogen and potassium. These findings returned to normal upon withdrawal of the neomycin.

In view of the similarity between these changes and those noted in non-tropical sprue, the present study was undertaken to characterize further the nature of the malabsorption induced by neomycin. For this purpose plasma carotene concentration has been used as a reflection of fat absorption while other absorptive parameters have been employed to define the range of malabsorptive errors induced by neomycin. These included glucose tolerance, iron-59 absorption, serum cholesterol and urinary excretion of D-xylose and of cobalt-60 labelled cobalamin.

These studies indicate that neomycin is responsible for a reversible type of malabsorption which affects a variety of materials normally absorbed from the small intestine. Although the significance of these findings in respect to the nutritional or therapeutic use of neomycin cannot be judged, it would appear that neomycin affords a useful technic for the study of malabsorption.

METHODS

The subjects were hospitalized patients without known gastrointestinal disease, except for three who had duodenal ulcer, three with hepatic cirrhosis and one with cholelithiasis. There were twenty-eight men and five women ranging in age from thirty-three to sixty-nine years. The diagnoses and the studies per-

formed are summarized in Table 1. Altogether, forty-five studies were completed on thirty-three subjects. The patients were fed regular hospital or low salt diets and neomycin was given as tablets or as a solution, † 12 gm. of neomycin sulfate being administered in three divided doses daily. Paregoric and Kaopectate® were given intermittently when necessary to ameliorate the diarrhea which was produced by neomycin.

In the studies of plasma carotene, regular hospital diets were found by calculation to contain between 2,000 and 4,000 units of carotene per day and a supplement containing 10,000 units (6,000 µg.) of beta carotene dissolved in peanut oil was provided each day. Six subjects were studied during three periods of six to nine days each: control period, neomycin period and postneomycin control period. Plasma carotene levels were determined approximately three times weekly by the method of Yudkin [3].

For comparison with the patients given neomycin, three other subjects were given 25 gm. magnesium sulfate daily orally for an interval of one week. A fourth subject received 15 gm. magnesium sulfate and 30 cc. castor oil daily for six days.

The urinary excretion of D-xylose following the oral administration of a 25 gm. dose was measured in eight subjects before the administration of neomycin and after neomycin had been given for from three to six days. In three subjects the test was repeated at intervals of one or two weeks after withdrawal of neomycin. The method of Roe and Rice was employed to measure the five-hour urine D-xylose content [4].

In nine subjects serum cholesterol levels were obtained before the administration of neomycin and at the end of six days of neomycin therapy. A modified

† Generously supplied by The Upjohn Company, Kalamazoo, Michigan, as Mycifradin Sulfate. The tablets contained 0.35 gm. neomycin base per 0.5 gm. tablet. The solution was prepared from a powder containing either 66.7 or 50 per cent neomycin base. Hence, 12 gm. of neomycin sulfate represented 6 to 8.4 gm. neomycin daily. All preparations gave approximately the same effect.

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TABLE I
STUDIES IN SUBJECTS GIVEN NEOMYCIN

Subject	Hospital Diagnosis	Studies Performed*
A. D.	Bronchiectasis	CA
J. V.	Bronchiectasis	CA
J. R.	Pulmonary tuberculosis	CA
J. A. S.	Cervical vertebral syndrome	CA, GTT
A. J.	Osteoarthritis	CA, GTT
O. P.	Multiple sclerosis	CA
J. C.	Cervical vertebral syndrome	CA
J. D.	Cardiac failure	CA
P. F.	Meningioma and craniotomy	CA
J. I. S.	Multiple sclerosis	CA
R. M.	Bronchogenic carcinoma	B ₁₂ , Chol.
M. H.	Bronchogenic carcinoma	B ₁₂ , Chol., GTT
E. A. P.	Hepatic cirrhosis	B ₁₂ , Chol., GTT
C. B.	Myocardial infarction	B ₁₂ , Chol., GTT
R. L. †	Hepatic cirrhosis	B ₁₂ , Chol., GTT
N. D.	Duodenal ulcer	B ₁₂ , Chol.
D. S.	Cervical vertebral syndrome	d-X
F. L.	Duodenal ulcer	d-X
D. L.	Cardiac failure	d-X
L. D.	Cataracts	d-X
P. M. †	Duodenal ulcer	d-X
E. A. R. †	Arteriosclerotic heart disease	d-X
L. T. †	Hepatic cirrhosis	d-X
A. M. †	Cholecystitis	d-X
J. P.	Coronary artery disease	Chol.
E. I. P.	Coronary artery disease	Chol.
R. B.	Nephrotic syndrome	Chol.
S. A.	Thrombophlebitis	Fe 59
W. S.	Rheumatic heart disease	Fe 59
E. T.	Emphysema	Fe 59
H. F.	Fever of unknown etiology	Fe 59
E. C.	Cardiac failure	Fe 59
W. L.	Angina pectoris	Fe 59

* CA = Carotene absorption

B₁₂ = Schilling test

d-X = d-xylene excretion (urinary)

Chol. = serum cholesterol

Fe 59 = radioactive iron absorption

GTT = glucose tolerance test

† Female.

Schoenheimer-Sperry method for the determination of free cholesterol in the serum was used [5].

Plasma radioactive iron curves were carried out in the fasting state in six subjects following the ingestion of a solution containing 20 μ c. of iron-59 as ferrous citrate and 25 mg. of carrier ferrous sulfate. The values were expressed as counts per milliliter of plasma as measured in a scintillation well-counter. Prior to the administration of the iron-59, a serum iron value was

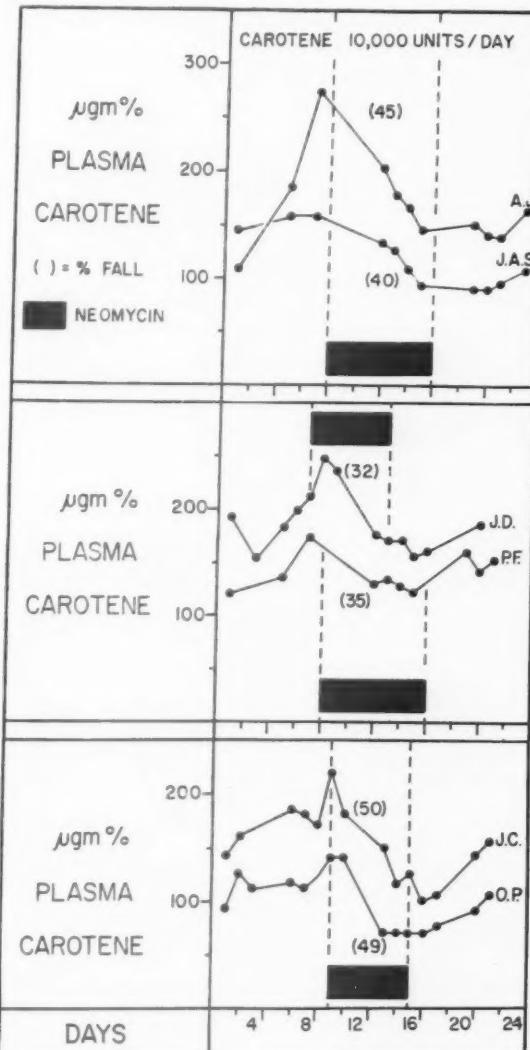


FIG. 1. Plasma carotene changes during the administration of neomycin.

obtained using the method of Kitze, Elvehjem and Schuette [6]. The plasma iron curve was obtained prior to the administration of neomycin and repeated directly following a three- to six-day course of neomycin. In all determinations the patient was studied at rest in the fasting state.

In six patients glucose tolerance curves were determined at intervals before and immediately after four to seven days of neomycin therapy. Repeat glucose tolerance tests were obtained in two of these subjects one week after neomycin therapy had been discontinued. Plasma glucose levels were determined by the methods of Somogyi [7] in four patients (M. H., E. A. P., C. B., R. L.) and Benedict [8] in two patients (J. A. S., A. J.), the same method being used for subsequent studies on any given subject.

The urinary excretion of vitamin B₁₂ was measured in six patients by the technic of Schilling, Clatanoff and Korst [9] using a forty-eight-hour urine collection. Studies were conducted before and just following an

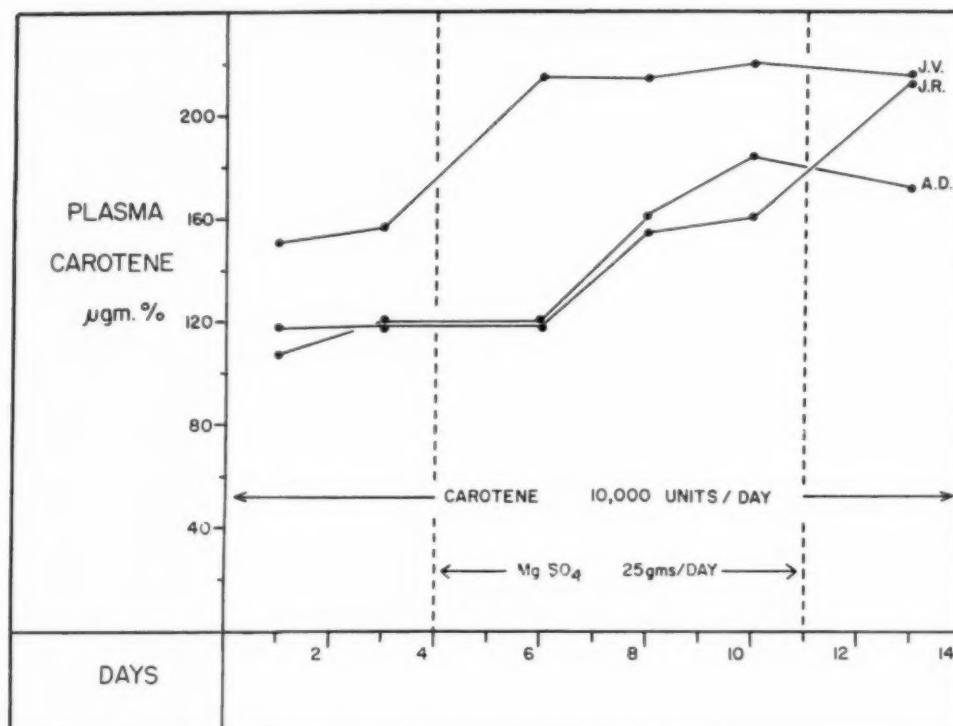


FIG. 2. Plasma carotene changes during the administration of magnesium sulfate.

interval of five to eight days of neomycin therapy. Urinary cobalt-60 vitamin B₁₂ was determined using a scintillation well-counter.

RESULTS

Carotene. In all six patients studied, a fall in plasma carotene concentration occurred during the administration of neomycin. (Fig. 1.) This decrease ranged from 32 to 50 per cent of the maximum concentration observed in each patient before treatment, and the degree of fall was accentuated by the fact that a rising concentration was observed prior to the administra-

tion of neomycin. In three subjects the carotene concentration during the period of neomycin therapy fell to borderline abnormal levels despite liberal intake of carotene. After the neomycin was withdrawn, the carotene levels showed no further fall or resumed the rising trend noted in the first control period.

By contrast, the effect of cathartic agents upon plasma carotene was not marked. Three patients to whom magnesium sulfate was given exhibited no decrease in carotene concentration (Fig. 2), and the subject receiving magnesium sulfate and castor oil showed a fall in carotene concentration which was less than that seen with neomycin. (Fig. 3.)

D-Xylose. Urinary excretion of D-xylose was lowered in seven of eight subjects during neomycin administration. (Fig. 4.) Three of these had urinary excretion values during the period of neomycin administration which were below the range of normal. The urinary D-xylose excretion was again determined in two subjects one week after discontinuance of neomycin and in one subject at one- and three-week intervals following withdrawal of the drug. The effect of neomycin was reversed in two of these three subjects upon cessation of treatment but persisted for at least three weeks in the third patient. (Fig. 4.)

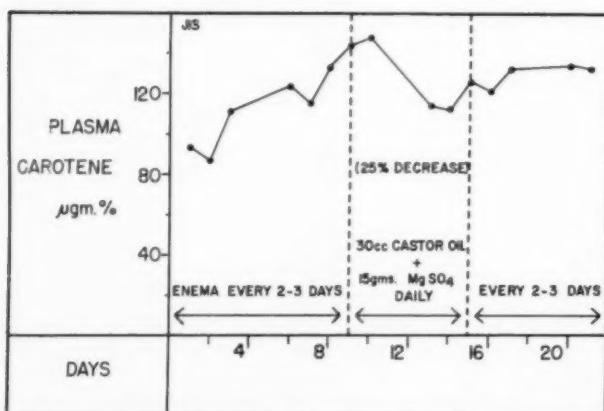


FIG. 3. Plasma carotene changes during the administration of castor oil and magnesium sulfate; 10,000 units of beta-carotene given daily throughout the study.

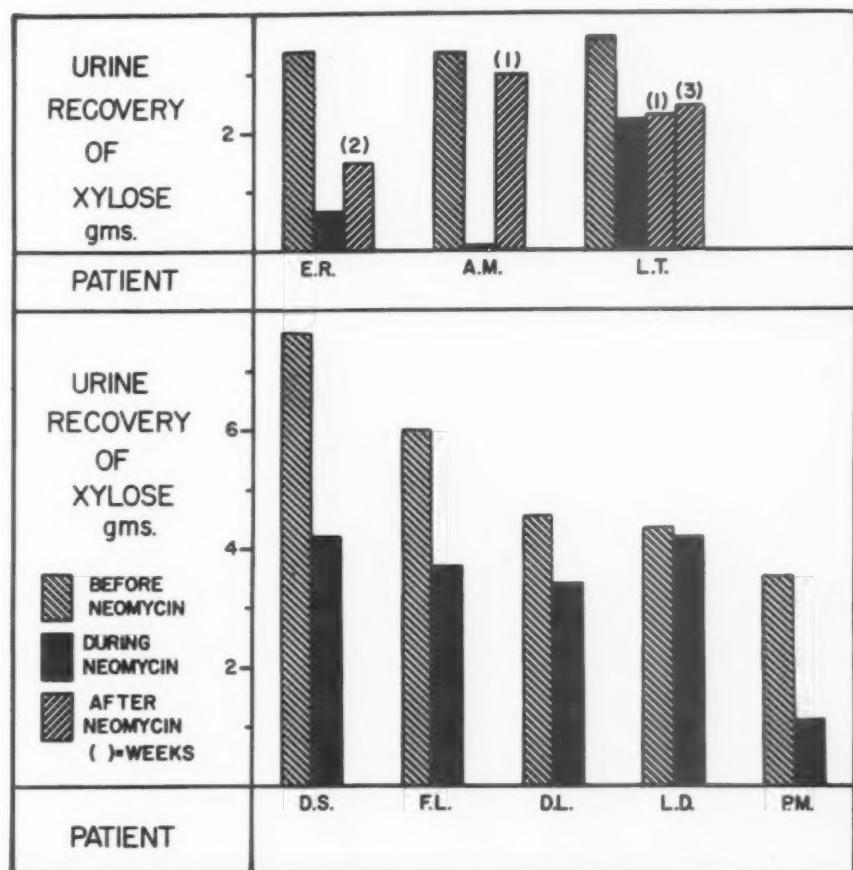


FIG. 4. Effect of neomycin upon the urinary excretion of D-xylose (control mean = 3.8 gm., S.D. = ± 1.7 , S.E. = ± 0.49 . Neomycin mean = 2.5 gm., S.D. = ± 1.3 , S.E. = ± 0.46 , p value = <0.1).

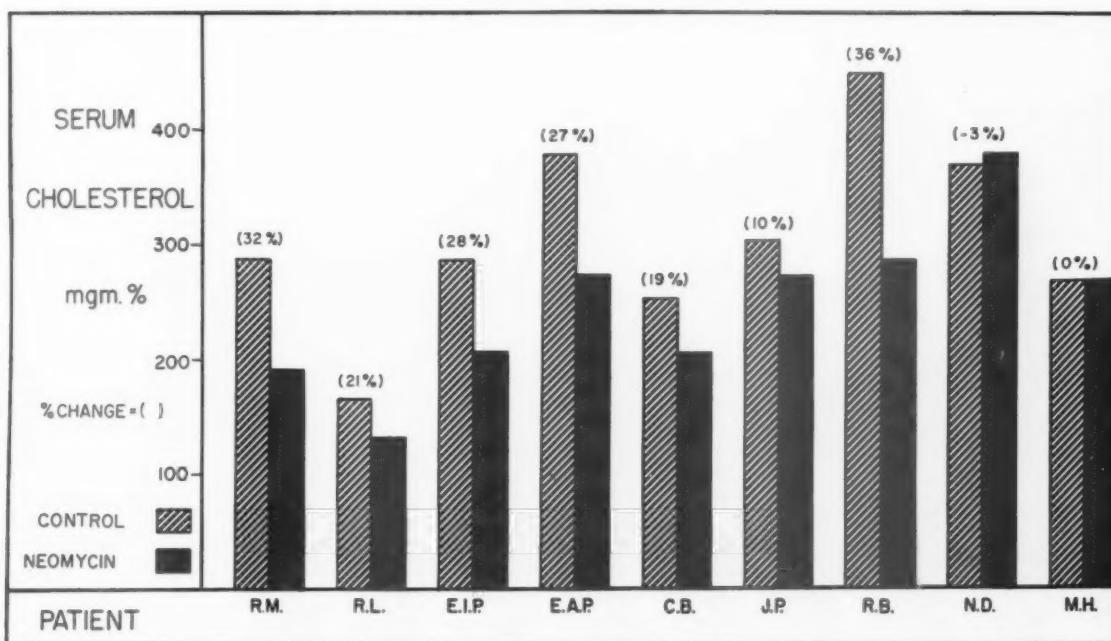


FIG. 5. Effect of neomycin administration upon serum cholesterol levels.

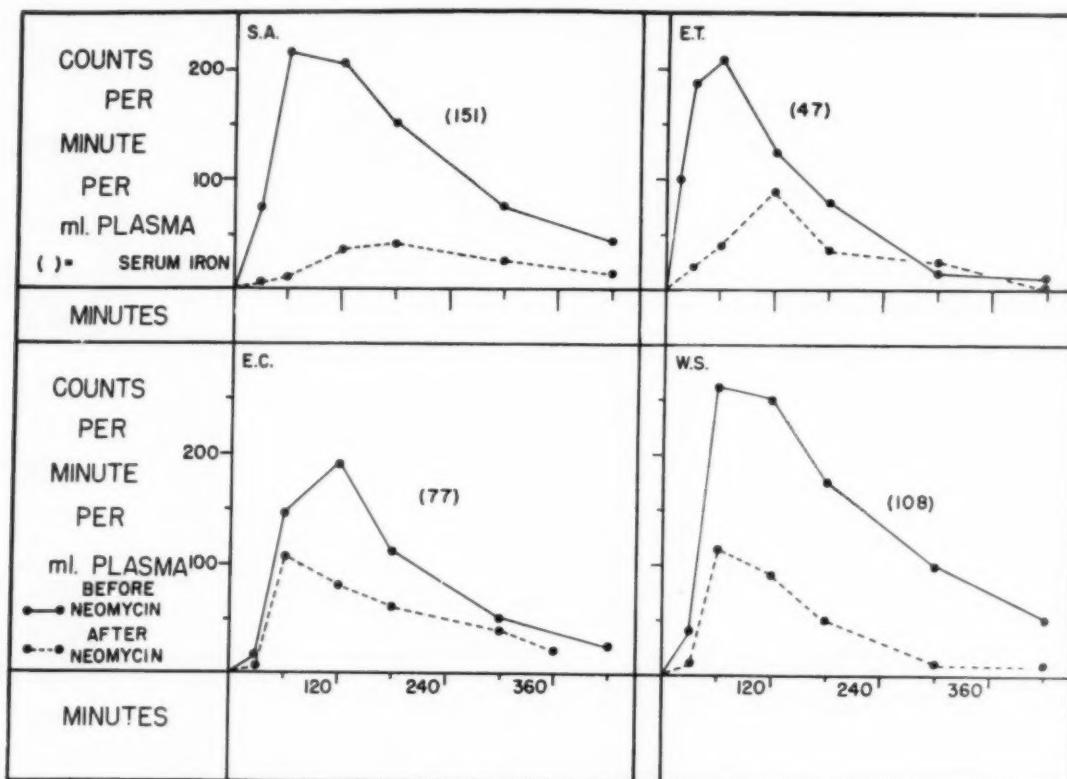


FIG. 6. Iron-59 absorption before and on the last day of the neomycin period. Note decrease in absorption in these four patients. Figures in () = serum iron in micrograms per cent.

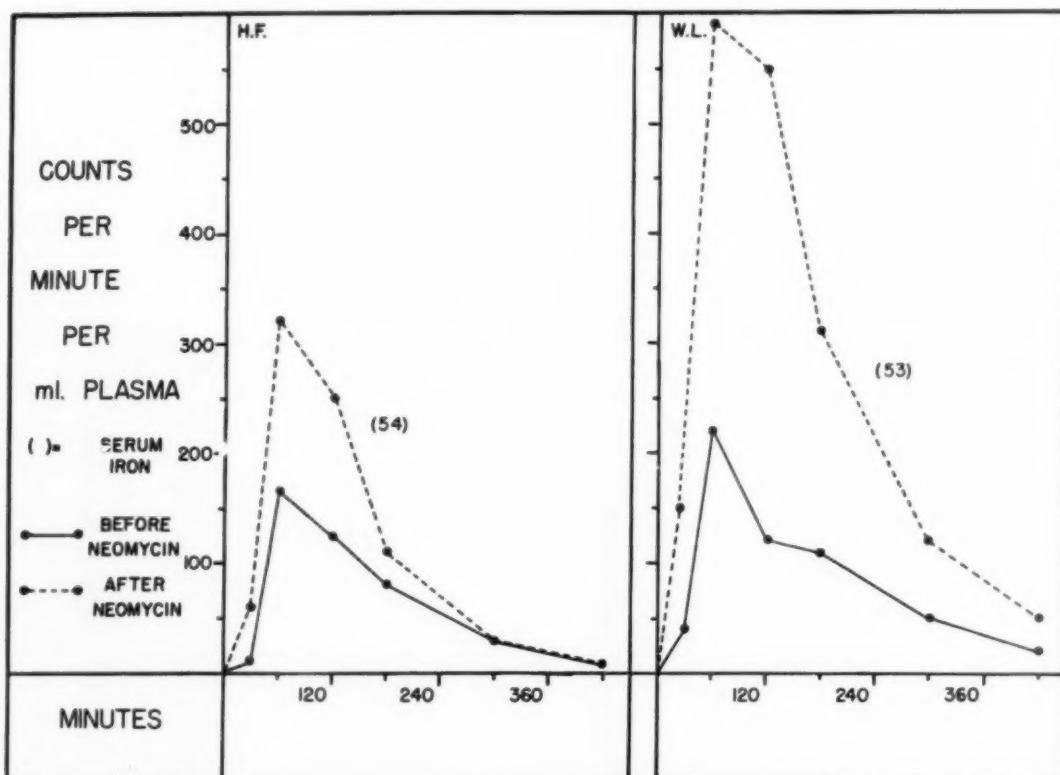


FIG. 7. Iron absorption before and during neomycin therapy. Note increase in absorption in these two patients.

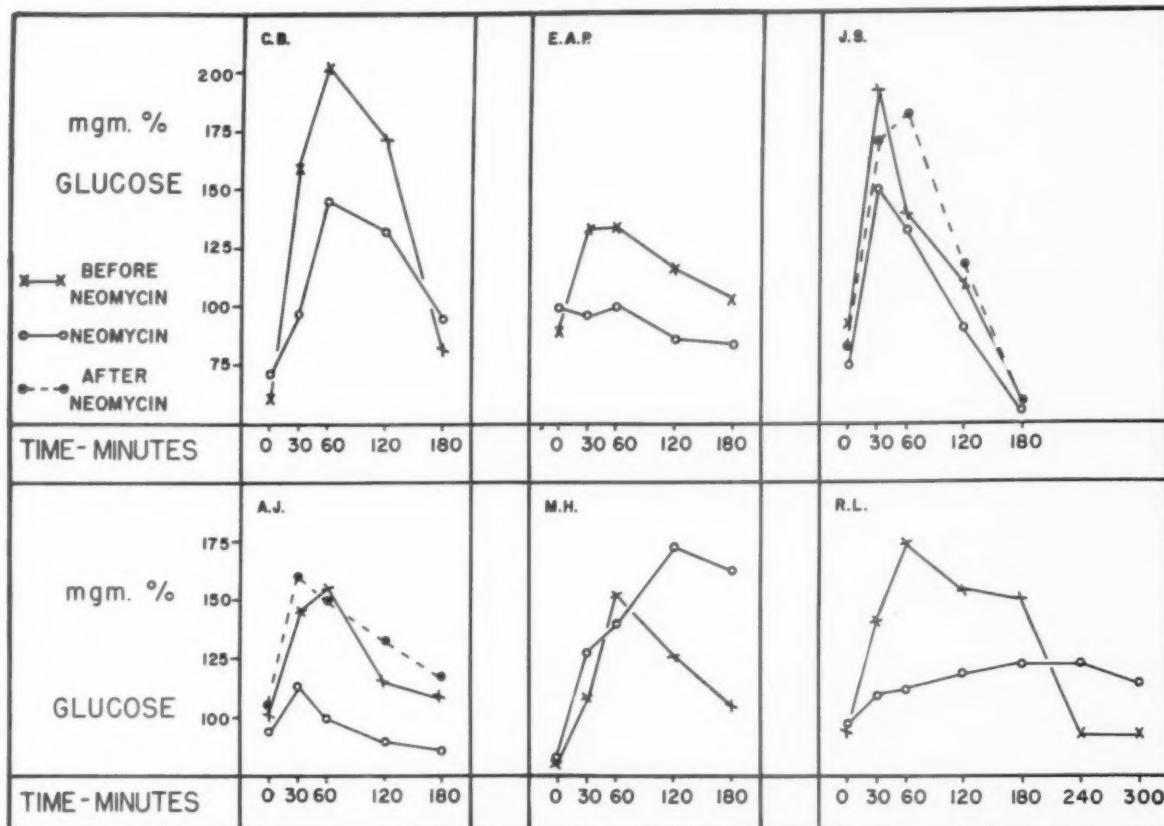


FIG. 8. Effect of neomycin administration upon glucose tolerance.

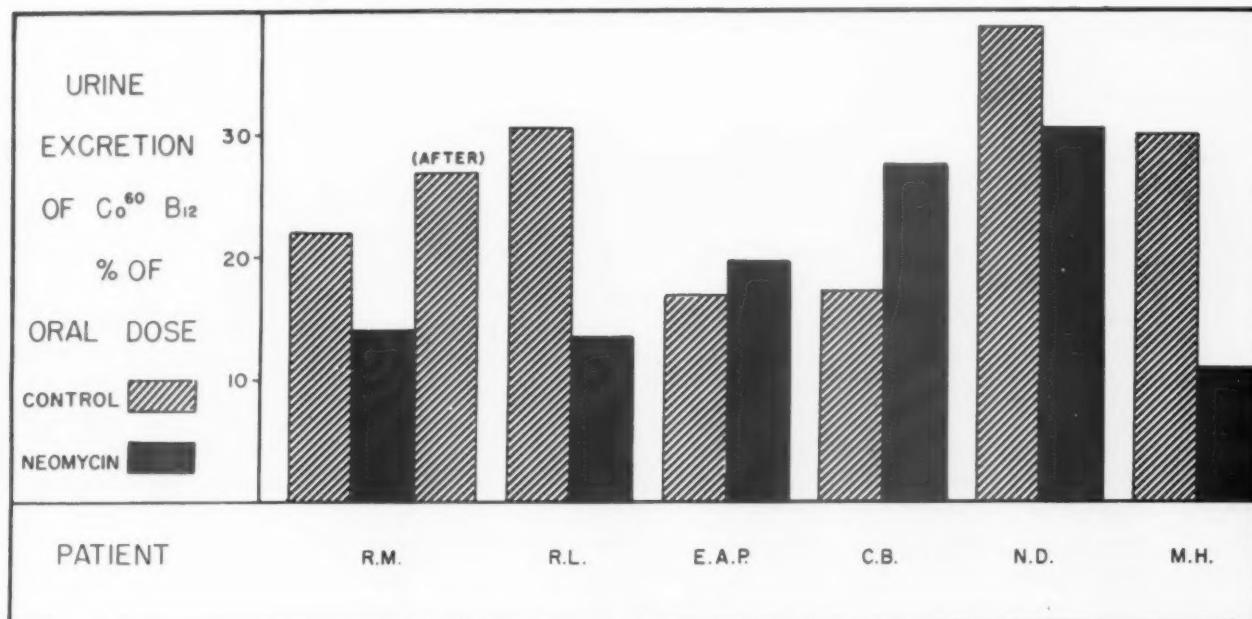
FIG. 9. Effect of neomycin administration upon urinary excretion of Co^{60} vitamin B_{12} (control mean = 26.3 per cent, S.D. = ± 7.7 , S.E. = ± 8.5 . Neomycin mean = 19.3 per cent, S.D. = ± 8.4 , S.E. = ± 11.9 , $p < 0.1$).

TABLE II*
COMPARATIVE ABSORPTION DEFECTS

Defect	Non-tropical Sprue	Neomycin Syndrome
Steatorrhea (fatty acids and soaps)	+	+
Azotorrhea	+	+
Increased stool calcium	+	±
Increased stool potassium	+	+
Decreased plasma carotene	+	+
Decreased urinary cobalamin excretion	+	+
Decreased iron absorption	+	+
Impaired glucose absorption	+	+
Decreased urinary D-xylose excretion	+	+
Decreased serum cholesterol	+	+
Positive nitrogen balance	+	+
Increased stool sodium	+	±

* See references 1, 2, 10 and 11.

Cholesterol. The serum cholesterol values fell from pretreatment levels in seven of nine subjects when neomycin was given. (Fig. 5.) In five of these seven the decrease exceeded 20 per cent and in a sixth subject was 19 per cent.

Iron Absorption. Curves of plasma radioactive iron concentration at selected time intervals following the ingestion of iron-59 labelled ferrous citrate were diminished in four of six subjects at the end of the period of neomycin administration as compared with the control measurements. (Figs. 6 and 7.) Two subjects who did not exhibit lowering of plasma iron concentration curves (Fig. 7) were found to have initially low serum iron levels. None of the subjects were anemic. One patient (E. T.) appeared to exhibit a delayed peak level while receiving neomycin.

Glucose Tolerance. Marked lowering of glucose absorption during neomycin administration occurred in four of six subjects. (Fig. 8.) Three of these four (A. J., E. A. P. and R. L.) had flat absorption curves when neomycin was given, and the fourth (C. B.) had a normal absorption curve during neomycin treatment although his control curve was diabetic in type. Of the two subjects not exhibiting marked lowering of absorption curves when neomycin was administered, one (J. S.) had a slightly lowered curve in the neomycin period which was not diabetic, while those obtained before and after the test

period achieved peak values which were in the diabetic range.

Vitamin B₁₂ Excretion. Four of the six subjects in whom cobalt 60-labelled vitamin B₁₂ absorption was studied demonstrated decreased urinary excretion of vitamin B₁₂ while receiving neomycin. (Fig. 9.) In two of these (R. L. and M. H.) the urinary excretion was less than half of the control value. In no subject did the urinary excretion of vitamin B₁₂ approach limits considered pathologic.

COMMENTS

The similarity between non-tropical sprue and the syndrome associated with the administration of neomycin is striking, as can be seen from Table II. In both syndromes there are varying degrees of interference with the absorption of a large variety of essential nutrients. The absorptive errors demonstrated in these studies would suggest that the absorption of other substances probably is also inhibited. As demonstrated by the prompt changes in carotene levels, it appears that the effects of neomycin are rapidly evident and furthermore are reversible in most patients within a few days.

The variety of absorptive errors induced by neomycin do not, of themselves, define the precise mechanism of its action. Several possible ways in which the drug could act include: (1) hypermotility of the bowel allowing insufficient time for absorption, (2) alteration in types or numbers of bacteria within the small bowel, (3) interference with mucosal intracellular enzyme systems, (4) inflammatory changes in mucosal cells with physical blockage of absorption and (5) combinations of several mechanisms.

Diarrhea is an extremely common side effect of neomycin therapy, even in doses smaller than those used here, and probably reflects general acceleration of the passage of materials through the small and large bowel. This hypermotility alone might account for decreased absorption per unit time, with no actual impairment of the mucosal absorptive mechanisms. That castor oil is capable of causing malabsorption has been reported elsewhere [12] and is suggested by the observations in one of the subjects (J. I. S.) in this study. However, evidence of malabsorption also was found in occasional patients who were constipated during periods of neomycin ingestion. Furthermore, the failure of magnesium sulfate to affect absorption of carotene in the face of severe diarrhea suggests that hypermotil-

ity *per se* is not the major factor in the production of carotene malabsorption.

Neomycin may induce malabsorption through its marked effect upon the bacterial flora in the intestine. In the dosage given in this study neomycin has been reported to inhibit bacterial growth almost completely, as determined by stool culture [13]. Diarrhea has also been observed following the oral administration of other antibiotics and has been attributed to changes in bacterial flora. These agents, however, have not been found to produce steatorrhea [14-16]. Another form of intestinal malabsorption, which is presumed to be caused by alterations in the composition of the gut flora, is seen in the "blind loop syndrome." Correction of this absorptive defect occurs with the administration of chloramphenicol but not with the administration of neomycin [17]. In this situation it appears that the use of neomycin may be tantamount to substituting one type of malabsorption for another. Furthermore, the bacterial content of the small bowel is normal in tropical sprue and celiac disease [18,19].

The metabolic processes involved in absorption could be affected by neomycin by direct interference with the biochemical function of the mucosal cells. In this sense neomycin could be considered to act as an enzyme poison. On the basis of available evidence this thesis is as unprovable as it is attractive. Furthermore, this would hypothesize that neomycin acts on a number of enzyme systems in order to account for its widespread malabsorptive effect, and it would not explain the ability of the drug to impede the transfer of such relatively freely diffusible materials as electrolytes [2].

Another explanation for the mechanism of the experimental malabsorption produced by neomycin is that the antibiotic exerts a direct inflammatory effect on the small intestinal mucosa rendering it less permeable to the passage of foodstuffs. That it does cause diarrhea and hypermotility is evident, and it probably does so in a manner analogous to that of irritant cathartics like castor oil. If this hypothesis is tenable, it could be anticipated that jejunal biopsies should show diffuse inflammatory changes early in the course of neomycin-induced malabsorption.

In the absence of strong evidence supporting either hypermotility, enzymatic poisoning or bacterial alteration, and with some evidence against each of these hypotheses, the most likely

explanation of these findings appears to be inflammation of the jejunal mucosa.

Our experience with the technics used herein to define the action of neomycin on absorption indicates that carotene absorption is the most sensitive qualitative method of evaluating neomycin effect and parallels the marked steatorrhea that neomycin initiates [7]. Conditions that could conceivably interfere with the validity of the results in this type of investigation include myxedema and jaundice [20]. None of these were noted in the subjects used in this study. These studies also indicate that the response to neomycin, as measured by daily carotene levels, occurs within twenty-four to forty-eight hours. Following the cessation of neomycin administration, however, a lapse of up to five days may occur before the neomycin inhibition of carotene absorption has subsided sufficiently to allow the supplemental carotene intake again to produce a rise in the plasma level. Lastly, it would appear that the blockage of carotene uptake from the gut by neomycin must be nearly total. If an individual is deprived of all carotene for one week, his plasma levels will approach abnormal limits [20]. A week-long course of neomycin in these studies was sufficient to lower normal pretreatment levels to borderline values in half the subjects despite the use of carotene supplements, thus indicating the severity of the carotene absorptive error produced by the drug.

Although the average excretion of D-xylose during the administration of neomycin is not significantly different from the excretion during control periods in the same patients, the changes observed in individual patients is great enough to indicate a real effect upon absorption. Such factors as duration of exposure to neomycin and individual resistance to its effect must be considered. Furthermore, it should be emphasized in regard to such other absorption parameters as vitamin B₁₂, iron and cholesterol, as well as D-xylose, that marked individual variation in occurrence and severity of the absorption errors is commonly observed in non-tropical and tropical sprue [11,21].

It was anticipated that serum cholesterol levels might be lowered by a course of neomycin, inasmuch as the drug causes marked steatorrhea and serum cholesterol levels have been observed to be depressed in tropical sprue [21]. The significance of change observed, however, depends upon the variation inherent in cholesterol

determinations and the spontaneously occurring changes in cholesterol levels encountered in any one patient. The method employed for cholesterol for these studies has been found in our hands to have a reproducibility of 10 per cent. It was therefore concluded that a decline in serum cholesterol of less than 20 per cent would not be considered significant in this study. A further deterrent to emphasis of these cholesterol alterations is our observation that patients receiving regular hospital diets frequently tend to exhibit some degree of fall in serum cholesterol with time.

The use of plasma iron concentrations as a parameter of absorption is open to the serious limitations imposed by the several factors other than absorption which control the plasma iron level [22]. These factors, which were all free variables in this study, include plasma volume, bone marrow activity, body iron stores and plasma iron levels. These variables were minimized by the use of patients whose hematologic status was constant, each patient thus serving as his own control.

The use of cobalamin excretion in the urine as a parameter of malabsorption is limited by two factors: (1) many patients with naturally occurring malabsorption states have normal values when tested by this method [18]; (2) the error for successive urinary radioactive cobalamin determinations in normal subjects can be up to 25 per cent [23].

The failure to find a statistically significant difference in the average absorption between the neomycin period and the control studies is, therefore, not surprising. Once again, however, the magnitude of the change observed in at least half the subjects studied is suggestive of a real effect of neomycin.

The therapeutic implications from this study are several. Neomycin is frequently used in the treatment of hepatic coma [13], in the therapy of bacterial diarrhea and in preoperative preparation of the intestine. In view of the short periods of neomycin administration, which are usually employed, the clinical significance of the malabsorption observed in these and previous studies cannot yet be assessed. The hazards of prolonged therapy, however, are perhaps indicated by these results.

That neomycin diminishes the absorption of iron and cholesterol is suggested by these studies. Whether these actions of the drug bear important implications in the treatment of hemo-

chromatosis or hypercholesterolemia is not evident on the basis of the data presented. It is of note that small doses of neomycin have also been reported to produce significant decreases in serum cholesterol levels [24].

It would appear that neomycin provides a means for altering intestinal absorption which may be of value in studies of intestinal function. This compound is poorly absorbed from the gut and pseudomembranous enterocolitis associated with staphylococcal infections has not been observed with its use. The malabsorptive errors which it induces appear to be corrected within a short time after its withdrawal. The possible relationship between this syndrome induced by neomycin and various malabsorptive states such as tropical and non-tropical sprue and celiac disease, however, is not clear. It should be possible to conduct further studies of the mechanisms involved in these disorders with safety.

SUMMARY

In an attempt to characterize the effect of neomycin upon intestinal absorption, six absorptive parameters have been employed: plasma carotene, urinary D-xylose excretion, serum cholesterol, plasma iron-59 curves, glucose tolerance and urinary excretion of Co⁶⁰-labelled vitamin B₁₂.

In six patients receiving supplementary carotene, the oral administration of neomycin for six to eight days produced a marked decrease in plasma carotene concentration. Following withdrawal of the neomycin the carotene concentration again rose. Comparison studies with magnesium sulfate catharsis were carried out in three subjects and revealed no fall in carotene levels. One subject receiving castor oil and magnesium sulfate showed a decrease in carotene levels which was less than that observed with neomycin.

Iron-59 absorption curves during the administration of neomycin showed decreased absorption, in comparison to control studies, in four of six subjects.

The urinary excretion of Co⁶⁰-labelled vitamin B₁₂ was reduced by 20 to 60 per cent of control figures in four of six subjects.

The urinary excretion of D-xylose after the oral ingestion of a test load decreased 35 per cent or more from control values in six of eight subjects during the period of neomycin administration.

In four of six subjects so studied, lowered glucose tolerance curves were observed; in three of these the curves became flat during the administration of neomycin.

The serum cholesterol concentration fell 19 per cent or more from control levels in six of nine subjects after five to eight days of neomycin therapy.

These findings indicate that neomycin is capable of producing a broad spectrum of malabsorptive errors resembling those observed in idiopathic steatorrhea.

Acknowledgment: We are indebted to Dr. James A. Halsted for valuable criticism and technical assistance in the studies of vitamin B₁₂ excretion; to Kathleen Duggan, Patricia Wood, Suzanne Samolis, Susan Hibbs, Jean Carroll, Raymond Wells, Jr. and Arckie Canton for technical assistance; and to Marthana Hjortland for dietetic assistance.

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The Differential Effect of Drugs on the Proximal and Distal Colon*

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IN recent years the intraluminal pressures in the normal rectum and sigmoid colon have been extensively studied by investigators using both balloon and open-tip recording technics [1], but very little is known about the motility of the less accessible proximal colon, and the simultaneous motility of the two areas. The available data suggest that the proximal and distal halves of the colon respond differently to pharmacologic agents [2,3], and that autonomic imbalance or disorder may be a basis for abnormal colonic function. After studying the normal phasic activity of the two sides of the colon, we attempted to document further the presence and nature of a differential drug effect. This paper reports simultaneous pressure measurements made in two colonic segments 40 cm. apart, using a perforated polyvinyl tube connected to an external electrical transducer system.

EXPERIMENTAL METHOD AND DESIGN

Initially, pressures were recorded in the various colonic segments, noting the basal pressures, the phasic activity and the characteristics of the phasic waves. The effects of various drugs upon the colon were then observed, using parasympathomimetic agents with different mechanisms of action, a parasympatholytic agent, and 5-hydroxytryptamine. Methacholine (Mecholyl®), which is rapidly hydrolyzed by cholinesterase and is basically similar in action to acetylcholine, was first employed. After obtaining a differential effect with Mecholyl, a cholinesterase inhibitor, neostigmine, was employed to confirm and further to define this differential. Bethanechol (Urecholine®) was then selected, since this compound is relatively unaffected by the concentration of cholinesterase at neuroeffector sites. Elorine® was employed to determine its efficacy in depressing normal phasic activity in different parts of the colon, and its ability to affect activity induced by Mecholyl and Urecholine. Finally, the effect of a drug of highly complex

pharmacologic nature, 5-hydroxytryptamine (serotonin) was observed.

METHOD

A modification of the polyvinyl tube described by Blankenhorn and his associates [4] was prepared in 700 cm. lengths. A 40 cm. section 200 cm. proximal to the mercury bag was made radiopaque by threading with an opaque suture, and the ends of this section were marked by silver dura-clips. Three mm. long oval windows were cut into the tubing immediately adjacent to the clips, furnishing the openings through which pressure changes were recorded.

Studies were made in eleven women and five men. Their mean age was fifty-five (forty-one to sixty-five) years. The subjects were free of clinical, radiological or laboratory evidence of gastrointestinal disease. The polyvinyl tube was passed through the nose, and the progress of the tube through the intestinal tract was followed roentgenographically until the mercury bag was passed per rectum. The bag was then cut off, and the end of the tube taped to the patient's buttocks. Pressure measurements were made after a minimal interval of twelve hours, during which time the patients became accustomed to the presence of the tubing. Measurements were taken for one and a half to four-hour periods, starting one to two hours after lunch or breakfast. When the same subject was studied on two or more consecutive days, measurements were taken at the same time on each day. The subjects did not receive cathartics, enemas or rectal examinations of any kind from the time that the tubing was passed until after the studies had been completed. Immediately before the recordings, a plain film of the abdomen was taken. If the two windows in the tubing were not in the desired positions in the colon, tubing was gently withdrawn from below, under x-ray control, until they were in the proper areas. (Fig. 1.)

The records were made with the subjects lying comfortably on a cot. The two ends of the tube were connected to Sanborn 267-A pressure transducers, and the system was perfused with distilled water. (Fig. 2.) The pressures exerted through the windows in the

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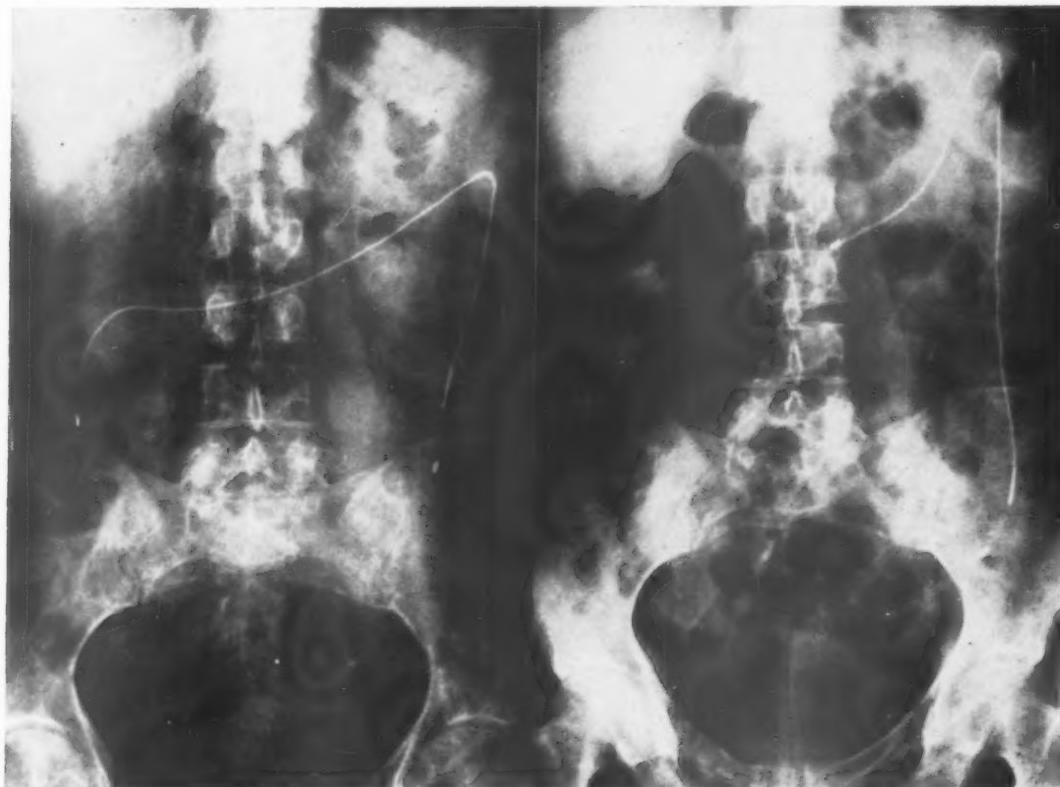


FIG. 1. Roentgenograms showing polyethylene tubes in position. Left, clips next to openings are in cecum and descending colon. Right, clips in transverse colon and sigmoid.

tube were recorded by a Poly-Viso recorder equipped with strain-gauge amplifiers. In an *in vitro* experiment, the damping and delay of an 8 fr. tube 700 cm. in length was determined by means of a series of syringe-induced rapid pressure changes. One limb of a Y tube was connected to a transducer through a 700 cm. length of tubing, while the other limb was connected directly to a second transducer. At the recording speeds used in this study (0.25 and 0.5 mm. per second) a maximal delay of one second was noted. Since the most rapid cyclic variations in pressure

currently recognized as bowel contractions have a frequency of 1 per four to five seconds [1], the one second delay is not considered significant. When pressure changes were induced over an interval of more than four seconds, loss due to damping was less than 8 per cent.

RESULTS

Pressure Changes During Control Periods. The pressure in the proximal colon was measured in twelve subjects for a total of fourteen hours. A

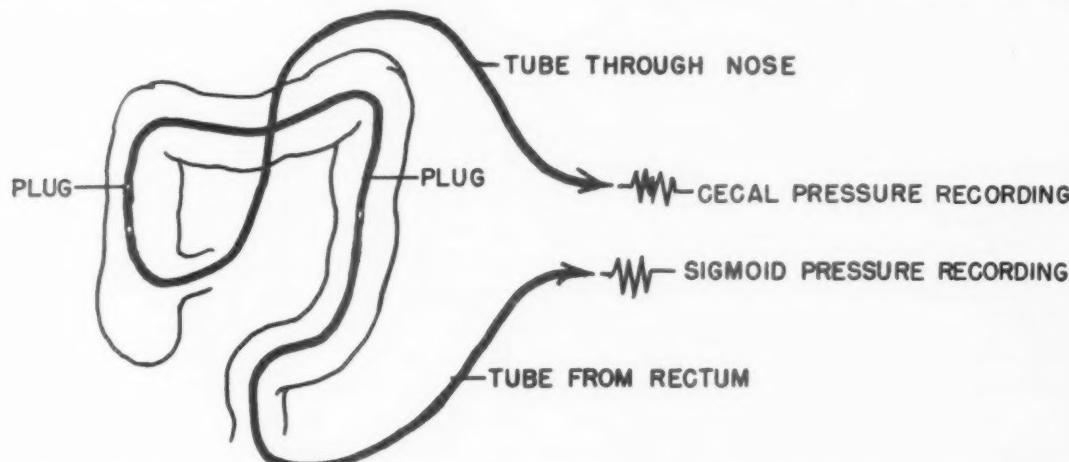


FIG. 2. Technic for simultaneously recording the intraluminal pressure from the proximal and distal colon.

TABLE I
THE EFFECT OF VARIOUS DRUGS UPON THE PRESSURE IN THE COLON

Drug	Systemic Effect	Proximal Colon Effect	Distal Colon Effect
Mecholyl (5 subjects)			
5-10 mg. subcutaneously.....	2+	2+	None
Mecholyl (3 subjects)			
10-12.5 mg. subcutaneously....	4+	4+	2 to 4+
Urecholine (1 subject)			
5 mg. subcutaneously.....	2+	2+	2+
Urecholine (6 subjects)			
10 mg. subcutaneously.....	4+	4+	4+
Neostigmine (3 subjects)			
0.75 mg. subcutaneously.....	1+	2+	None
Neostigmine (2 subjects)			
1.5 mg. subcutaneously.....	3+	3+	3+
Serotonin (12 subjects)			
1.5 mg. intravenously.....	4+	4+	Depressed
Elorine (6 subjects)			
10 mg. subcutaneously or intra-venously.....	1+	Depressed	Depressed

marked variation in the number of phasic waves per hour was noted in different subjects, with waves present from 10 to 60 per cent of the time. The majority of the waves lasted from ten to thirty seconds and occurred in an arrhythmic fashion. Other waves occurred in rhythmic sequences lasting from three to fifteen minutes, at rates varying from 3 to 6 per minute. The wave amplitudes ranged from 3 to 40 cm. of water, with a mean amplitude of 15 cm. The pressure changes in the left transverse colon, splenic flexure, descending and sigmoid colon were recorded for a total of sixteen hours in twelve patients. The phasic waves resembled those seen in the proximal colon, differing only in the rate of rhythmically appearing waves, which never exceeded 3 per minute. Pressure changes in the rectum were recorded in eight subjects for a total period of eight hours. The phasic activity of the rectum differed from that of the upper distal colon in that waves were present only about ten per cent of the time and, when present, were usually of longer duration (one to two minutes) and of greater amplitude (mean 25 cm.) than those recorded in the descending colon.

It was found that activity in the proximal colon occurred independently of that in the distal colon, and that the converse was also true. It was not possible to correlate coincident or subsequent pressure changes in the proximal colon with changes in the distal colon, or to correlate waves seen in the left transverse colon with sigmoid or rectal waves.

In all the subjects similar basal pressure values were noted in the proximal and distal colon, with a maximum difference of 1 to 2 cm. The basal pressures ranged from 8 to 12 cm. of water, with a mean value of 10 cm. The basal pressures did not vary during the baseline observation periods.

The Effect of Drugs upon Intraluminal Pressure (Table 1). Injections of saline solution (1 cc. subcutaneously) were given ten minutes before the injections of the other drugs. These injections did not significantly affect the records in any of our subjects.

The comparative effects of Mecholyl were studied in the ascending and descending colon (four subjects), ascending colon and rectum (four subjects) and left transverse colon and rectosigmoid (three subjects).

The systemic effect of Mecholyl (5 to 12.5 mg. subcutaneously) varied greatly from subject to subject. When the systemic effect was mild, proximal colonic motility was definitely increased, but distal motility increased slightly or not at all. The effect upon colonic motility was characterized by an increase in the number and amplitude of the phasic waves, which lasted for five to ten minutes. When the dose of Mecholyl caused a severe systemic reaction, not only was the proximal colon stimulated but increased activity was registered also from the rectum in two subjects, and from the sigmoid colon in a third. (Figs. 3 and 4.) Mecholyl did not decrease phasic activity in any part of the colon in our subjects. The highest pressure recorded after the administration of Mecholyl was 70 cm. of water in the proximal colon, and 95 cm. in the distal colon.

Neostigmine, 1.5 mg., stimulated both sides of the colon when given to two subjects. In one subject, the effect of three different doses of neostigmine on the ascending and sigmoid colon was observed at the same time of day on three consecutive days. On the first day the subcutaneous injection of 0.75 mg. of neostigmine increased the phasic activity of the proximal colon, but did not increase that of the distal colon. On the second day, 1.5 mg. of neostigmine stimulated both sides of the colon, and on the third day, 1 mg. of neostigmine stimulated the proximal colon, and had a slight effect upon the distal colon. (Fig. 5.) The colonic pressure changes were more gradual in onset than those seen after the administration of Mecholyl; they occurred from twenty to thirty minutes after the injections, and lasted for ten to twenty minutes.

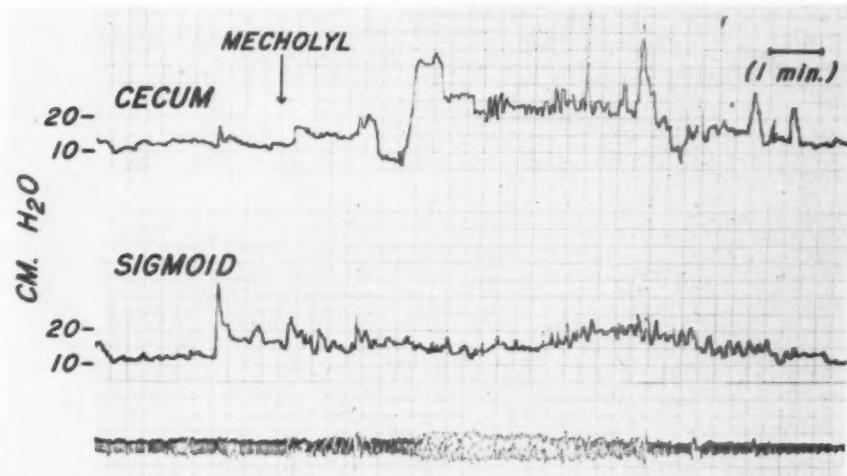


FIG. 3. The effect of 10 mg. of Mecholyl on the cecal and sigmoid intraluminal pressures. Patient had a mild systemic reaction to this dose. (Bottom tracing is pneumographic recording.)

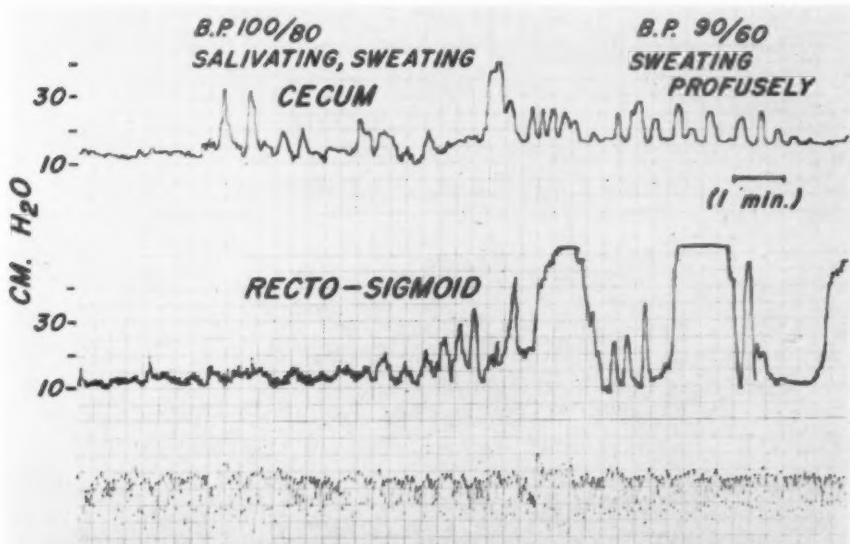


FIG. 4. The effect of 12.5 mg. of Mecholyl on the intraluminal pressure. Patient had a marked systemic effect from this dose.

In five other subjects, injections of 0.75 and 1 mg. of neostigmine had little or no effect upon the sigmoid.

The effect of Urecholine (10 mg. subcutaneously) on the ascending and sigmoid colon was observed in four subjects, and on the left transverse colon and rectum in two others. Urecholine consistently increased the phasic activity in all the areas tested. The injection of 5 mg. in one subject caused a more moderate, equal increase in phasic activity on both sides of the colon. The amplitudes of the phasic waves corresponded to those demonstrated with Mecholyl. In addition, one subject had a rise of 15 cm. in the cecal basal pressure, accompanied

by severe cramps and abdominal pain. Basal pressures in the other subjects were not affected by the administration of Urecholine or the other drugs tested. In two subjects continuous pressure recordings were obtained over a four-hour period during which the administration of 10 mg. of Mecholyl was followed, after one and a half hours, by the injection of 10 mg. of Urecholine. Both drugs strongly stimulated the proximal colon in each instance but the effect of Urecholine on the distal colon was greater than that produced by Mecholyl.

The simultaneous effect of Elorine upon the two sides of the colon was observed in seven subjects. The subcutaneous or intravenous

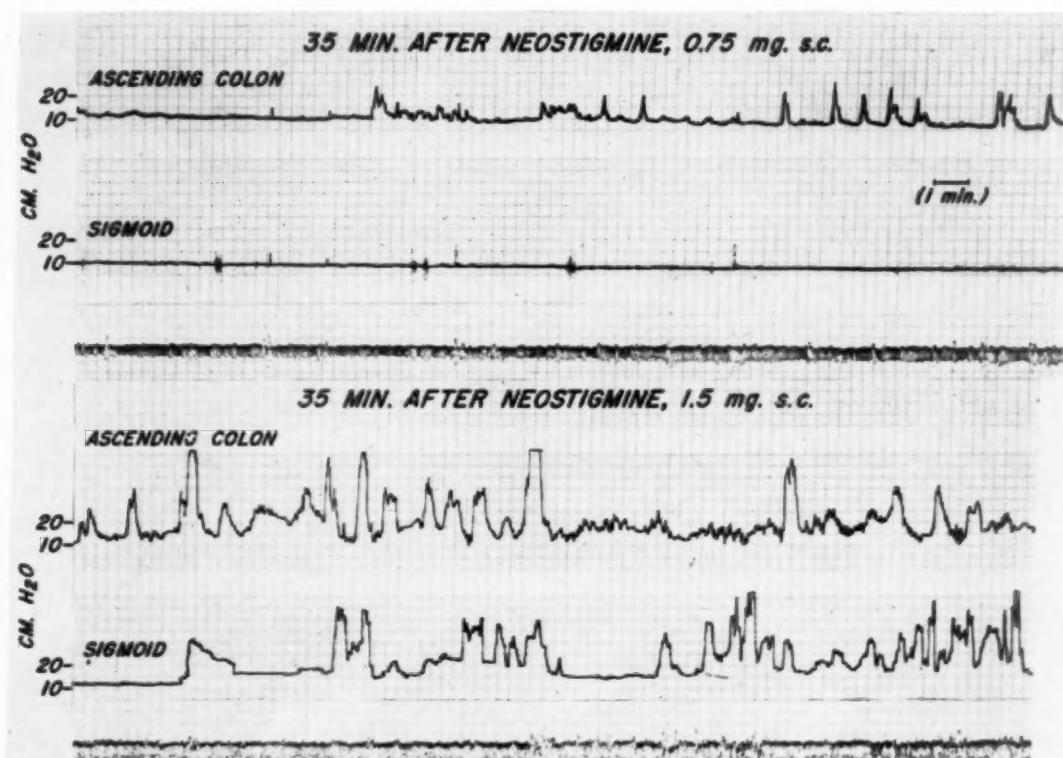


FIG. 5. The effect of two different doses of neostigmine, given twenty-four hours apart, on the same patient.

administration of 10 mg. of Elorine depressed spontaneous motility and motility induced by Mecholyl and Urecholine. Upon questioning, two patients stated that their mouths felt dry after intravenous injection of Elorine. No other side-effects were noted.

The effect of serotonin upon the ascending and descending colon was noted in five subjects, and in the descending colon and rectum

in seven others. Rapid intravenous administration of 1.5 mg. evoked a brief systemic response characterized by a facial flush, constriction in the chest and coughing. Serotonin increased the phasic activity of the proximal colon and depressed that of the distal colon. (Fig. 6.) Serotonin stopped spontaneous distal colonic motility, and motility induced by the prior administration of neostigmine. In the latter instance, the end of the period of serotonin effect was sharply demarcated by the sudden return of neostigmine-augmented phasic activity.

Locus of Change in Response. Measurements made with the tube opening in the transverse colon showed that diminished sensitivity to Mecholyl began in the area immediately to the left of the mid-transverse colon. Figure 1 (right) shows the location of a tube during an experiment in which 10 mg. of Mecholyl was given with marked systemic effect. Increased bowel sounds were heard, indicating increased activity elsewhere in the gastrointestinal tract, but the phasic waves were not increased at either of the two recording sites. Openings in the left transverse colon also failed to register increased phasic activity in three other subjects to whom 5 to 10 mg. of Mecholyl was given.

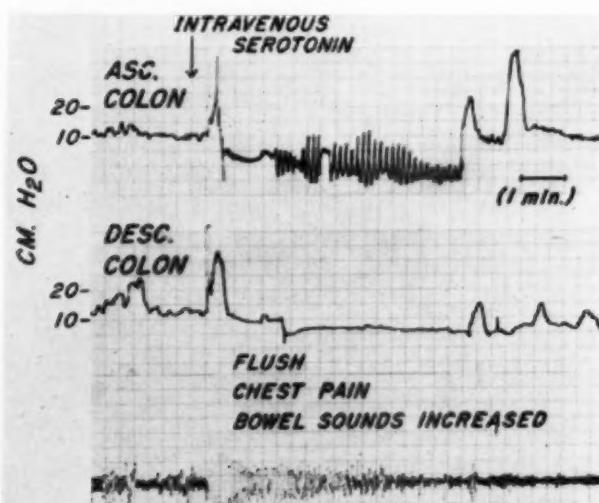


FIG. 6. The effect of intravenous serotonin on the motility of the two sides of the colon.

COMMENTS

An ideal system for recording the activity of a gut segment should utilize an accurate, sensitive recording device which will not alter the activity of the area by its presence. Our use of thin, flexible tubing, the open-tip recording technic, and an external electronic recording system represents a close approach to this ideal. The open tip makes possible accurate measurements without distention of the bowel, and complete transintestinal intubation by the thin tubes makes it possible to study any part of the bowel without the presence of fistulas.

The waves recorded in the proximal colon correspond to the wave types I and II which have previously been described in the pelvic colon [5]. Following the administration of cholinergic drugs a few isolated type III waves were seen in the proximal colon; none were seen in records of spontaneous activity. Type IV waves, described in subjects with ulcerative colitis [7], were not seen at any time.

The subcutaneous administration of Mecholyl in doses ranging from 5 to 10 mg. evoked distinct proximal colonic activity, but had little or no effect on the distal colon. This differential effect was abolished when higher doses of Mecholyl (10 to 12.5 mg.) were used. With these doses a marked systemic response occurred coincident with increased proximal and distal colonic phasic activity. The difference in effect of autonomic agents on the ascending and descending colon suggested either a difference in the number and type of smooth muscle units, a difference in the concentration of cholinesterase (CHE), or other factors involving differences in reactivity to humoral sympathetic agents. Small doses of neostigmine stimulated the proximal colon but had no effect on the distal segments. Doubling the dose of neostigmine markedly stimulated both the proximal and distal colon.

Reviewing the two series of experiments, it is suggested that the concentration of CHE in the distal colon may be greater than that of the proximal colon. The fact that Mecholyl in moderate dosage stimulated the right colon and not the left could be related to a higher concentration of CHE on the left, allowing more rapid dissipation of Mecholyl effect. The use of small doses of neostigmine prompted stimulation of the proximal colon, perhaps by tying up the limited supply of CHE in that area, while the

same dose had little effect on the left colon, where an abundance of CHE may have been present. If this hypothesis is correct, cholinotropic drugs (acting directly on neuroeffector cells) should have a similar effect on both the proximal and distal segments. An equivalent stimulating effect on both the proximal and distal segments was repeatedly obtained with Urecholine, a drug unaffected by CHE.

Kern et al. [2] have reported simultaneous motility tracings from the cecum and sigmoid of a patient with a transverse colostomy, using the balloon technic. Following the subcutaneous administration of 5 mg. of Mecholyl, these workers demonstrated augmented cecal activity and cessation of sigmoid motility. In a separate communication by these same authors [3] only two of sixteen patients receiving a continuous infusion of acetylcholine showed enhancement of distal colonic activity, while the other subjects showed equivocal or depressed distal colonic activity. We did not observe depression of distal colonic activity after the administration of Mecholyl. Depending upon the dose of the drug, motility was either unaffected or enhanced. Two factors may account for the apparent differences in these results: (1) A variation in drug effect due to differences in degree of sigmoid tone at the time of stimulation. In the reports cited, patients were fasted for six to twelve hours and prepared with several saline enemas prior to the administration of the drugs. No such preparation was given the patients in our study. (2) Possible interference by balloons with the venous return in the stretched area. It has been shown that stretching of the bowel may modify or even reverse the effects of stimuli [6]. No such interference could occur in our experiments employing thin polyvinyl tubes.

Balloon-kymograph studies have shown that Elorine is an inhibitor of sigmoid motility [7]. Our data confirm these findings and indicate that Elorine depresses proximal colonic activity as well. We noted no untoward reaction to the drug and its efficacy in depressing motility suggests that Elorine may be of clinical value.

It is difficult to explain the action of serotonin in the light of present knowledge. Serotonin has been shown capable of both exciting and depressing jejunal motility [8] and our data also suggest that the drug does not have a simple cholinergic or adrenergic effect on the bowel. Further studies of the effect of serotonin on the sigmoid, alone and in combination with cholin-

ergic, anticholinergic, and ganglionic-blocking agents, appears indicated.

Abundant anatomical data confirm earlier suggestions that the vagus supplies parasympathetic preganglionic fibers to the proximal half of the human colon, and that the nerve fibers arising from the second and third sacral nerves are distributed to the descending colon and rectum [9]. X-ray evidence suggests that the vagus innervated and sacral innervated colon are two functionally distinct units, with the point of demarcation in the area of "Cannon's point" [10,11]. It is interesting to note that our division of the colon into two areas based upon a difference in reaction to drugs corresponds closely to the division made by the alleged "point" or "contraction ring." Our findings support the view that the colon should be considered composed of two segments, a proximal segment and a distal one, with the division in the transverse colon, at or close to the mid-line.

SUMMARY

Simultaneous intraluminal pressure measurements were made in separate colonic segments of sixteen human subjects. The amount and characteristics of the basal and phasic pressures in different parts of the colon are described. The effects of selected drugs upon the intraluminal pressure are also noted. Small doses of Mecholyl and neostigmine selectively enhanced the phasic activity of the proximal colon, but did not affect the distal colon. Large doses of these drugs increased phasic activity in both the proximal and distal colon. Urecholine consistently increased both proximal and distal colonic phasic activity. Serotonin stimulated the proximal colon, but depressed distal colonic motility. Elorine depressed spontaneous and

drug-induced phasic activity in both areas. The difference in the effect of autonomic agents on the ascending and descending colon suggest that the concentration of cholinesterase in the distal colon is greater than that of the proximal colon.

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Erythrocyte Dynamics in Liver Disease*

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A COMPLETE understanding of the erythrocyte dynamics of a particular disease requires knowledge of the rate at which red cells are produced, of the rate at which they are removed from the circulation, and of the balance that is maintained, or the red cell volume. The latter has been well studied in patients with liver disease by several investigators [1-6]. Low, normal and elevated red cell volumes have been found in cirrhosis.

Red cell destruction has been studied in patients with liver disease. Chaplin and Mollison [7] and Jandl [8] measured the survival of normal erythrocytes transfused into patients with disease of the liver, and found increased destruction in all patients studied. Jones et al. [9] and Allen et al. [10] measured the radioactive chromium (Cr^{51}) half-time of the patients' own cells transfused back into patients with hepatic disease; both groups found approximately one-third of the patients to have a shortened cell survival, one-third to be borderline, and one-third to have a normal red cell survival. No one has attempted to determine whether or not there is a shortening of potential erythrocyte life span as a result of inherent cell defects associated with hepatic disease.

In patients with chronic congenital hemolytic syndromes Crosby and Akeroyd [11] found an increase in the rate of erythrocyte production to several times the normal rate in partial or complete compensation for the increased rate of cell destruction. The degree of compensation for the increased rate of cell loss in liver disease has not been studied. There are two basic approaches to the measurement of erythrocyte production. One, used by Crosby and Akeroyd [11], is a calculation based on red cell volume and red cell life span. The second includes a variety of direct measurements of either effective or total erythropoiesis by such methods as examination of the bone marrow, reticulocyte count, removal of iron from plasma and red cell utilization of

radioactive iron. With the exception of the measurement of plasma iron turnover in acute viral hepatitis by Peterson [12], the more exact methods of measuring erythropoiesis have been applied in only an occasional patient with hepatic disease.

The purpose of the present study was to obtain a more comprehensive picture of the red cell dynamics in patients with liver disease, with emphasis on erythropoiesis, the aspect not previously studied. The primary concern of the study was to determine alterations of erythrocyte dynamics in the presence of significant hepatic dysfunction which could possibly affect erythropoiesis by either a quantitative limitation of production or the production of cells which age rapidly. Such factors as the effects of the ingestion of alcohol and malnutrition were of secondary concern. Consequently, the studies were initiated after patients had abstained from alcohol and had been taking a good diet for at least two weeks; several patients with hepatic disease who either had never been alcoholic or at least had not been drinking for several years were included.

METHODS

Subjects. The patients studied were males with impairment of hepatic function of moderate to marked degree. Twenty-five had alcoholic cirrhosis; two, prolonged acute infectious hepatitis; one, chronic infectious hepatitis; and one, extensive liver replacement with metastatic carcinoma. The diagnosis was proved by biopsy in ten and at autopsy in four; in the remainder of patients the clinical and laboratory findings were typical, leaving little or no doubt as to the diagnosis. All were in relatively stable states of their disease during the period of study. All the cirrhotic subjects had abstained from alcohol and had been on hospital diets for at least two weeks prior to initiation of the study. With the exception of those studied by radioiron, the patients with cirrhosis were unselected provided none of the following were present: (1) a history of hemorrhage within four

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months, (2) any blood in the stool by repeated benzidine testing, and (3) disorders other than disease of the liver known to have abnormal hematologic manifestations. Red cell volume and short-term red cell survival were measured in five normal male medical students as a check on the methods used.

Total Red Cell Volume. The red cell volume was determined by the Cr⁵¹ method of Read [13] with the following modifications. (1) The blood was incubated with the Cr⁵¹ for twenty minutes. (2) An ACD solution (Abbott) manufactured for red cell chromation was used as an anticoagulant. (3) Post-transfusion samples were obtained at ten and twenty minutes. For labeling, 100 to 125 μ c. of high specific activity Na₂Cr⁵¹O₄ were used, and the concentration of chromium injurious to red cells was not approached. The red cell volume was calculated by the equation:

$$\text{RBC Volume} = \frac{\text{Unit activity transfused blood (counts/minute/ml. RBC)} \times \text{vol. RBC given (ml.)}}{\text{Unit activity 10 minute sample (counts/minute/ml. RBC)}}$$

The volume in each case was related to body weight, which may be somewhat in error in patients with a disturbance of the normal ratios of muscle:bone:fat:viscera, but the volume must be related in some way to body size. The dry weight was used in the calculations if fluid retention was present. This was determined by weighing the subject after fluid loss resulting from improvement or paracentesis, or after removal of fluid at autopsy, or by estimation based on weight before the development of ascites. The presence or absence of varices was determined by clinical, roentgenographic, esophagoscopy or splenopertigraphic examination, or at autopsy. The results were compared with the group of normal males studied by Huff and Feller [14]. This group was selected because it is the largest in the literature, and it is similar to the present series in sex (all males), method of calculating results and range of body sizes. The mean red cell volume of five normal male medical students studied in our laboratory was almost identical with that obtained by Huff and Feller.

Red Cell Survival. The survival of the red cells chromated for determination of the red cell volume was followed as described by Read et al. [15]. Samples were taken until at least two-thirds of the initial radioactivity (with correction for decay) had disappeared, and the average point of termination of sampling was 15 per cent of initial activity. The resulting survival curves were analyzed by the method of Eadie and Brown [16], using their equation:

$$(1) \quad N_t = N_0 \left(1 - \frac{t}{T}\right) e^{-kt}$$

Where:

N_t = Radioactivity on day t, corrected for decay.

N₀ = Corresponding count on day zero.

T = Potential life span in absence of external hazards.

k = k₁ + k₂ = Fraction radioactivity lost per day from all types of loss exclusive of age.

k₁ = Fraction radioactivity loss per day from elution of chromium.

k₂ = Fraction radioactivity loss per day from random cell destruction.

N_t was determined experimentally. N₀ was determined by plotting values of N_t, a linear semilog plot, for the first week and extrapolating to t = 0. T and k were determined as follows. Equation (1) can be expressed as:

$$(2) \quad \frac{N_0}{N_t} \left(1 - \frac{t}{T}\right) = e^{-kt}$$

and

$$(3) \quad \ln \left[\frac{N_0}{N_t} \left(1 - \frac{t}{T}\right) \right] = kt$$

which equation yields a straight line of slope k. A value for T was assumed for each patient. $\ln \left[\frac{N_0}{N_t} \left(1 - \frac{t}{T}\right) \right]$ was evaluated for each experimental value of N_t and t, and plotted for each value of t. If the resulting plot was not linear, a second value of T was assumed and the process repeated. By repetition of the process, a value of T was found which would give a linear plot and was considered to be the true value of T, and k was taken as the slope of the plot. T was determined to the nearest two days and is expressed in Table I to the nearest five days. T and k were determined for each patient. In three sets of data this process was compared with the least squares method used by Eadie and Brown [16]. The linear plot method was surprisingly sensitive and much less tedious but gave a fit as good as the least squares method or better. k₁ was assumed to be 0.009, the mean value found in normal subjects by both Eadie and Brown [16] and by Ebaugh, Emerson and Ross [17]. k₂ was found by k - k₁ = k₂.

Having determined the parameters indicated, it was necessary to calculate the actual mean life span of the red cells in each case. This was carried out by a method Dornhorst [18] suggested for situations in which both random destruction and senescence contribute to cell loss. Values of N_t corrected for elution were determined by: $N_t = N_0 \left(1 - \frac{t}{T}\right) e^{-kt}$ using T and k₂ as determined. The expression $\frac{N_t \text{ [corrected]}}{N_0 \left(1 - \frac{t}{T}\right)}$

was evaluated and plotted for each value of t, and the area of the curve between t = 0 and t = T was measured. The mean cell life was taken as the area divided by the initial height.

Red Cell Production. The rate of production was calculated by the equation: Daily red cell production

TABLE I*

RED CELL VOLUME, SURVIVAL AND PRODUCTION AS MEASURED BY RADIOPHORUM

Patient	Brom-sulphalein (%)	Serum Bilirubin (mg. %)	Serum Albumin (gm. %)	Red Blood Cell Volume (ml./kg.)	T (day)	k_2	Mean Cell Life Span (day)	Red Blood Cell Production	
								(ml./day)	(ml./kg./day)
<i>Patients with Cirrhosis</i>									
J. De.	..	22.6	2.2	21.1	75	0.011	50	18.8	0.236
F. D.	24	1.3	2.2	29.8	70	0.012	50	23.6	0.41
J. Fi.	28	1.9	2.3	23.1	70	0.011	50	49.4	0.62
J. Dw.	37	4.4	2.5	34.6	120	0.015	55	36.4	0.47
J. Fa.	24	3.0	3.5	18.1	70	0.007	55	42.8	0.61
H. R.	..	5.9	3.2	27.0	75	0.008	55	22.8	0.32
P. Y.	35	3.2	2.5	31.3	90	0.009	60	37.8	0.50
W. M.	..	2.1	3.1	31.1	95	0.008	65	35.8	0.46
J. Fl.	38	3.0	4.7	26.4	75	0.000	75	36.6	0.35
P. P.	18	1.0	3.4	28.3	125	0.010	75	23.8	0.39
J. McD.	..	14.1	2.3	34.5	95	0.004	80	27.4	0.43
G. O.	14	1.2	4.2	20.5	95	0.004	80	15.4	0.26
W. S.	38	4.0	3.5	31.7	95	0.004	80	29.2	0.40
G. T.	13	1.7	4.7	24.5	125	0.009	80	23.8	0.31
M. C.	15	2.2	3.9	28.6	95	0.002	85	21.5	0.33
C. M.	37	3.1	3.0	25.5	125	0.006	90	21.6	0.28
R. P.	..	19.8	3.0	23.3	115	0.006	90	13.6	0.26
J. A.	18	3.5	28.8	120	0.004	100	16.0	0.29
Mean	27.1	96	0.007	71	28.0	0.40
<i>Patient with Prolonged Acute Hepatitis</i>									
H. G.	33	4.6	95	0.012	55
<i>Patient with Chronic Hepatitis</i>									
P.W.	8	0.6	4.0	25.2	100	0.011	60	28.2	0.41
<i>Patient with Metastatic Tumor</i>									
L. P.	..	5.6	3.6	25.0	65	0.012	45	25.3	0.56

*T—Potential erythrocyte life span in absence of external hazards.

k_2 —Fraction of erythrocytes lost per day from random cell destruction.

Figures in bold face type represent calculated normal values.

(ml./day) = $\frac{\text{Total red cell volume (ml.)}}{\text{Mean red cell life span (day)}}$. One hundred and twenty days, the figure used by Crosby and Akeroyd [17] in this equation, was taken as the normal mean life span of the red cell. The red cell volume data of normal subjects of Huff and Feller [14] were used in the numerator to calculate normal red cell production.

Plasma Iron Turnover and Red Cell Iron Utilization. Radioiron (Fe^{59}) studies combined with radiophosphorus studies were performed in a few patients using the method of Huff et al. [19] modified as

follows: (1) Fe^{59} ferrous citrate was used; (2) the iron was added to 50 to 60 ml. of whole blood in plastic bags after chromation of the red cells, and incubated for thirty minutes at 37°C ; (3) plasma volume was calculated from the red cell volume determined by the Cr^{51} method and the whole body hematocrit; and (4) serum iron was determined by the method of Peters et al. [20].

Counting Techniques. The Cr^{51} samples were counted in duplicate in 2 ml. volumes in either a well type scintillation counter with a scaler or in the same coun-

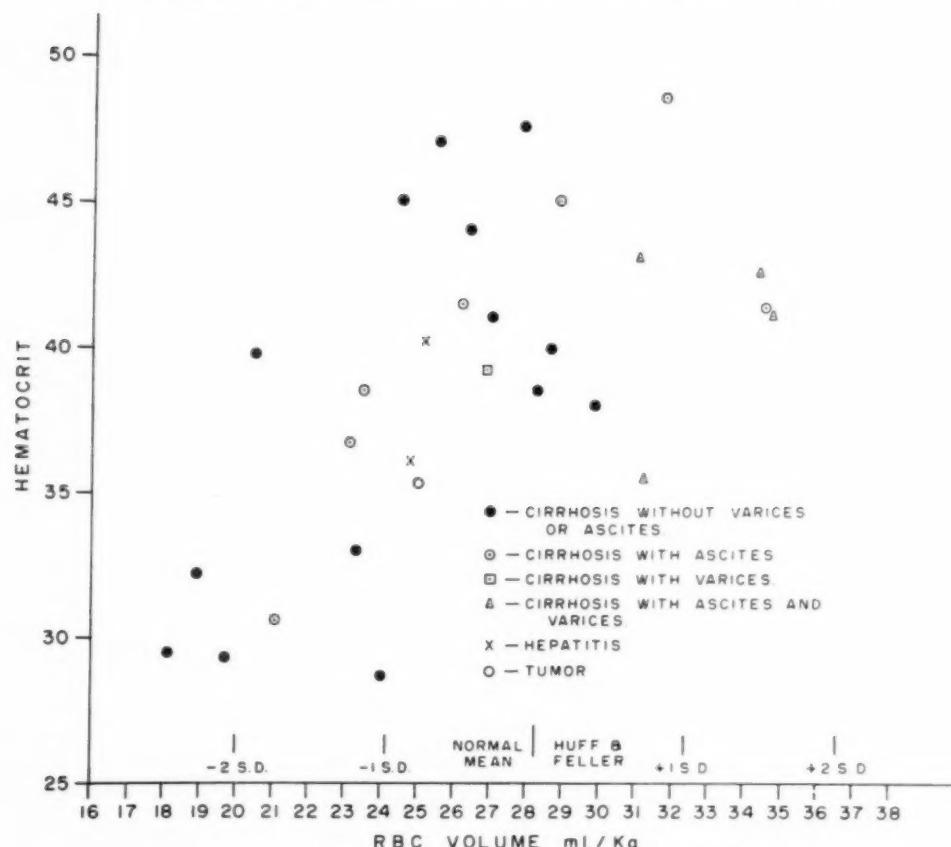


FIG. 1. Red cell volume of each patient compared with hematocrit.

ter used with a scintillation spectrometer. Samples of combined Cr⁵¹ and Fe⁵⁹ were counted in a Baird-Atomic Model 513 Scintillation Spectrometer.

RESULTS

Total Red Cell Volume. The red cell volume was measured in twenty-five patients with alcoholic cirrhosis and in three patients with other types of damage to the liver. One patient was studied twice, and both sets of data are

TABLE II
MEAN RED CELL VOLUMES OF VARIOUS SUBGROUPS

Group	No. of Cases	Mean and Standard Deviation		
		Red Blood Cell Volume (ml.)	Red Blood Cell Volume (ml./kg.)	Hematocrit
All hepatic disease.....	29	1,810 ± 420	26.3 ± 4.3	38.9 ± 5.5
All cirrhosis.....	26	1,860 ± 445	26.5 ± 4.9	39.1 ± 5.8
Cirrhosis without varices or ascites.....	14	1,740 ± 440	24.5 ± 3.6	38.1 ± 6.6
Cirrhosis with ascites.....	11	1,980 ± 390	29.1 ± 4.9	40.4 ± 4.5
Cirrhosis with varices.....	5	2,275 ± 250	31.6 ± 3.4	40.2 ± 3.4
Normal male subjects Huff and Feller [74]..	42	2,260 ± 370	28.3 ± 4.1	48.5 ± 3.0

included since there was a significant progression of his disease in the interval of one year.

The results are given in Table II and Figure 1. The mean volumes of the various groups of patients with hepatic disease expressed in either ml. or ml./kg. of body weight did not differ significantly from those of the normal group of Huff and Feller with the exception of the group of patients without ascites or varices (difference -3.8, standard error of mean 1.15). Three patients had red cell volumes 2 to 3 standard deviations below the normal mean and could be considered truly anemic. Figure 1 demonstrates the lack of close correlation between hematocrit and red cell volume. One of the three patients with a low red cell volume was a malnourished, severe alcoholic with moderate hepatic disease whose general condition improved considerably. Eight months later he had a relapse and at that time was found to have a partially megaloblastic bone marrow. He again responded without specific therapy. Another patient with pancytopenia and splenomegaly had cirrhosis, which was proved by biopsy but his liver function was relatively good. The

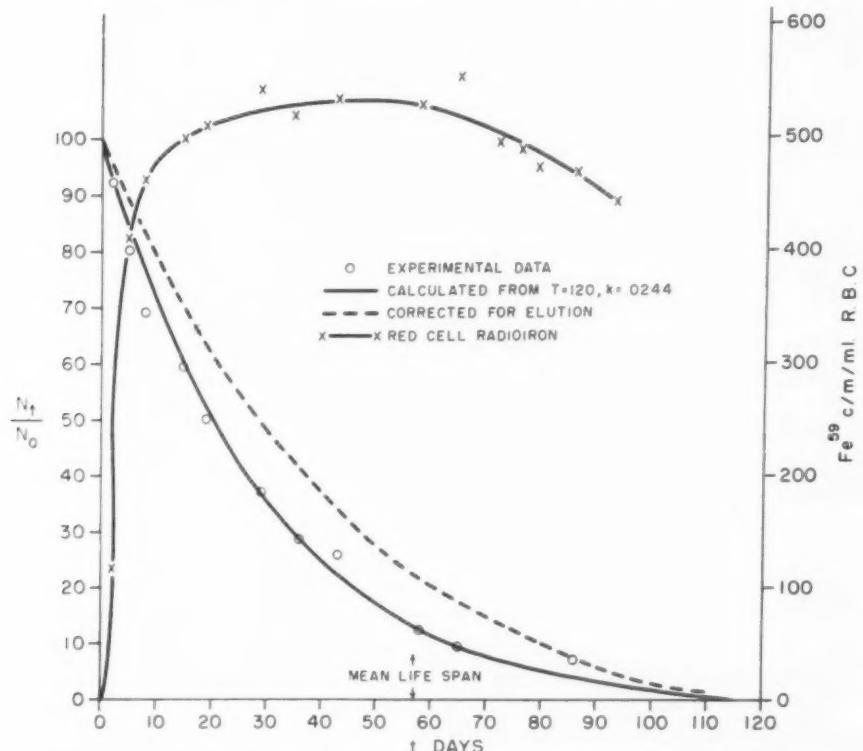


FIG. 2. Patient J. Dw. Erythrocyte survival curves. Curve of erythrocyte incorporation of Fe^{59} and loss of Fe^{59} from circulation. The Cr^{51} and Fe^{59} studies were performed simultaneously.

third patient had severe cirrhosis without unusual features.

Red Cell Life Span. Twenty-one patients, eighteen of them with cirrhosis, were followed up by blood sampling for a sufficient time to permit measurement of the erythrocyte life span. An attempt was made to follow up all patients except a few whose disease did not remain stable or who showed evidence of blood loss after the study was initiated; however, several were lost to follow-up through lack of cooperation. The data were treated as described under "Methods," and the results are given in Table I. Mathematically, the data could be carried to more significant figures than are given, but it was considered that biological limitations precluded this. Although many normal subjects have been studied by a variety of red cell survival techniques, neither the normal mean cell life span nor the standard deviation of the mean have been conclusively established. It appears likely that the normal limits of the mean are between 100 and 130 days and that the average mean is 110 to 120 days [27]. Eadie and Brown [16], using Cr^{51} as a label and the method of analysis used in the present study, found potential life spans of 126 and 109 days in two normal

subjects. The actual mean cell life span is the product of all factors acting to remove cells from the circulation. Under normal circumstances the average potential life span and the actual mean cell life span are the same. When random destruction is present, the actual mean cell life span is less than the potential.

The potential life span of the red cells excluding all environmental hazards was 115 days or greater in six patients with cirrhosis and can certainly be considered normal. It was between ninety and ninety-five days in six, and between seventy and seventy-five days in six others. The latter group was considered to have a shortening of the potential erythrocyte life span.

The measurement of red cell survival by radiochromium (Cr^{51}) is complicated by the loss of the label from the cell by what is assumed to be elution. Having obtained the constant k , which indicates the total rate of exponential loss of radioactivity, k_1 or the constant indicating the rate of elution was subtracted from k to determine k_2 . Seventeen of eighteen patients with cirrhosis had a k_2 greater than 0, thus showing evidence of random destruction of the red cell. (Table I.) It must be pointed out that rates of elution of normal subjects vary about the mean

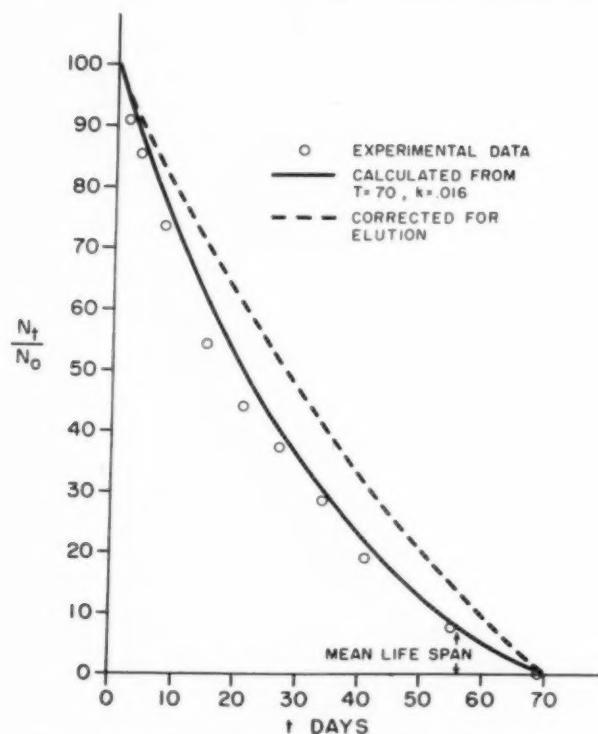


FIG. 3. Patient J. Fa. Erythrocyte survival curves.

of $k_1 = 0.009$. Eadie and Brown [16] measured k_1 in normal blood from two donors which was transfused to six recipients. k_1 varied from 0.006 to 0.011 with a mean of 0.009. Therefore, the use of $k_1 = 0.009$ when calculating $k_2 = k - k_1$ undoubtedly resulted in too high a value for k_2 in some cases and too low in others. These deviations will cancel out in averaging a series of this size, and the mean k_2 of the entire group of 0.007 is significant. Moreover, if the deviations from normal of individual calculated values of k_2 were simply an expression of the deviations of k_1 about the mean, half of the values of k_2 would be greater than 0 and half less. All but one value of k_2 was greater than 0.

The actual mean red cell life span ranged from fifty to one hundred days. (Table I.) Since the calculation involved the constant k_2 , some values in individual patients are undoubtedly too high and others too low. The mean of the entire group, seventy-one days, is considered reliable and significant. Illustrative survival curves from the data from two patients are given in Figures 2 and 3. The experimental data in both cases are compared with the curve resulting from the evaluation of $N_t = N_0 \left(1 - \frac{t}{T}\right) e^{-kt}$.

The second survival curve in each case is from the data corrected for elution by evaluating

$N_t = N_0 \left(1 - \frac{t}{T}\right) e^{-kt}$. The three patients with hepatic disease other than cirrhosis are listed separately in Table I. The findings were similar to those of the patients with cirrhosis in all respects.

Red Cell Production. The calculated normal values for red cell production of 18.8 ml./day and 0.236 ml./kg. of body weight/day are useful reference points, but the spread about these means is unknown. Consequently, it is difficult to determine the magnitude of deviation from the mean indicative of abnormality. All eighteen patients with cirrhosis listed in Table I had rates of production greater than 0.236 ml./kg./day. Two (J. Dw. and F. D.) had rates almost three times this figure, and the average rate of the group was 1.67 times the normal mean. It should be noted that all but one patient (J. Fa.) were able to increase production to compensate for varying degrees of shortening of cell life span, and maintained red cell volumes within the limits of normal.

Erythrocyte production was measured by radioiron (Fe^{59}) technics in a small group of patients selected to represent different manifestations of cirrhosis. The results are given in Table III. One patient (M. H.) had good hepatic function but a low normal red cell volume and macrocytosis. Another patient (T. G.) had only mild cirrhosis (proved by biopsy), but a long standing pancytopenia, assumed to be the result of hypersplenism, was present. The other three patients had severe cirrhosis, one with marked bilirubin retention. Cr^{51} survival studies were initiated in all but were terminated in three in two to three weeks for various reasons. One patient (W. D.) died following hemorrhage from a gastric ulcer, one (T. G.) had a hemolytic reaction from normal fresh blood on the fourteenth day, and the third (M. H.) was lost to follow-up. The fraction of iron removed per hour and the plasma iron turnover were normal or greater than normal in all cases. The incorporation of iron into the red cells was prompt and reached a high per cent of the given dose in all cases. A curve of red cell iron incorporation and of iron loss as the cells left the circulation is given in Figure 2.

COMMENTS

The findings of the present study do not necessarily apply to all patients with hepatic

TABLE III
RED CELL PRODUCTION AS MEASURED BY RADIOPRUE

Patient and Condition	Brom-sulphalein (%)	Serum Bilirubin (mg. %)	Serum Albumin (gms. %)	Cr ⁵¹ Studies			Fe ⁵⁹ Studies			
				Red Blood Cell Volume (ml./kg.)	Mean Cell Life Span (day)	Red Blood Cell Production (ml./kg./day)	Plasma Fraction Removed (per hr.)	Plasma Iron Turnover (μg./kg./hr.)	Mean Marrow Time (day)	Red Blood Cell Utilization
<i>Normal Subjects</i>										
Bothwell et al. [29]							0.48	18.3	3-4	82
Huff et al. [19]							0.41	14.6
<i>Present Series</i>										
J. Dw., cirrhosis, ascites, varices	37	4.4	2.5	34.6	55	0.61	0.39	15.8	3	86
W. D., cirrhosis, ascites	..	1.6	2.8	26.2	0.52	38.3	3	82
J. De., cirrhosis, ascites	..	22.6	2.2	21.1	50	0.41	0.69	47.8	3	77
T. G., cirrhosis, hypersplenism	3	1.5	4.3	19.7	2.77	192	2	76
M. H., alcoholism	3	0.5	3.9	22.3	0.55	15.1	3	83

disease. Such patients, particularly those with cirrhosis, exhibit a variety of clinical manifestations, and their erythrocyte dynamics may also be expected to vary. In addition, patients with alcoholic cirrhosis may have hematologic disorders which are not a consequence of liver damage *per se*. These include the syndrome of hemolysis, fatty liver and lipemia in acute alcoholism described by Zieve [22], and nutritional folic acid or vitamin B₁₂ deficiencies as described by Jandl and Lear [23] and by Krasnow et al. [24]. The patients in the present study had chronic disease, were in relatively stable stages of their disease during the study, and had been on good dietary programs for at least two weeks before initiation of the study. The conclusions drawn can be related only to this type of patient. The findings in the patients with chronic liver damage due to viral infection or tumor in no way differed from those with alcoholic cirrhosis, and the findings in those alcoholics who had been on good regimens for months or years did not differ from those of patients who had been drinking up to a few weeks before study. Consequently, all the patients will be discussed as a group.

A wide range of red cell volumes was found in this group of subjects with chronic liver disease. In the patients with esophageal varices and/or ascites red cell volumes tended to be high, findings similar to those of Eisenberg [6] who also correlated cyanosis in cirrhosis with a high red cell volume. No particular manifestation of liver disease has been correlated with a low

red cell volume. Incomplete information from the literature and from the present study suggests that reduced red cell volume may be found in the type of overt hemolytic syndrome described by Hyman and Southworth [25] (T. G., present study), in the type of hemolytic syndrome of alcoholics described by Zieve [22], and in the presence of associated dietary deficiency of folic acid and vitamin B₁₂ (J. H., present study). It appears well established by the work of others [1-6], and by the present study, that the incidence of true anemia in chronic disease of the liver is lower than originally believed. Frequently the apparent anemia is simply hemodilution by a high plasma volume.

The actual mean life span of the erythrocyte was found to be shortened by two processes, shortening of the potential life span presumably from inherent cell defects and from random cell destruction. Only one abnormality was present in some cases, and in others both processes were present in proportions that varied among patients. The increased senescence of erythrocytes from inherent cell defects has not been described previously. Further confirmation could be obtained by the measurement of survival of erythrocytes transfused from a patient with liver disease into normal subjects, but one is hesitant to transfuse blood from patients with hepatic disease. The pitfalls of mathematical analysis of data as used in the present study to determine the life span of the red cell and factors involved in its alteration are well discussed in the analytical reviews of Dornhorst [18] and

Eadie and Brown [27]. The survival curves obtained in the present study definitely differed from those found by others who studied normal subjects. The possible errors are in the analysis of the factors producing the abnormal curves. Undoubtedly there are errors in the expression of the magnitude of potential life span of the red cell or rate of random cell destruction in individual cases. However, the deviation from normal of these parameters is considerable in some instances, and the means of the entire group are abnormal. For these reasons, the conclusions herein stated regarding the life span of the red cell are considered valid.

The high incidence of macrocytosis associated with hepatic disease [26,27] suggested the possibility that these macrocytes had shortened potential life span. The mean erythrocyte diameter was measured in ten unselected patients of the group; all had macrocytosis. The potential life span in the group ranged from seventy to 120 days. It was concluded that the macrocytosis and increased senescence were not closely related.

The etiology of the random destruction of the erythrocyte was not clear. Splenomegaly has been suggested as a cause, but only a minority of the patients had splenomegaly, and several with high rates of random cell destruction did not have enlargement of the spleen. Chaplin and Mollison [7] demonstrated random destruction after splenectomy. The finding of hemolysis in patients whose disease was caused by factors other than alcohol or who had abstained for months or years rules out alcohol as the sole cause.

If a low hematocrit is taken as an indication of anemia in hepatic disease, one may falsely assume that erythropoiesis is impaired and that the patient cannot compensate for an increased rate of cell loss. Calculation of the rate of production from measurement of the red cell volume, as in the present study, indicated adequate production in the majority of cases. The rate of production did not approach the rate of six to seven times normal found by Crosby and Akeroyd [11] in patients with congenital spherocytosis. However, in all but one case the degree of increase in erythropoiesis was sufficient to compensate fully for the decrease in mean cell life span. Impairment of erythropoiesis might be anticipated in patients with impairment of protein synthesis, but a high rate of production was maintained in spite of severe

hepatic dysfunction, including impaired production of serum albumin and prothrombin in several instances.

The reader is referred to the articles by Bothwell et al. [28,29] for a complete evaluation of radioiron studies as measures of erythropoiesis. In brief, the plasma iron removal and turnover are related to total erythropoiesis; whereas the incorporation of iron into the red cell is related to effective erythropoiesis. The latter method is not satisfactory in evaluating hyperfunction. The Fe⁵⁹ studies tended to support the conclusion drawn from the calculation of red cell production from the volume and survival data. Total and effective erythropoiesis were normal or increased in all instances, and in one patient (T. G.) reached a very high level. Jandl [8] considered that alcohol might impair erythropoiesis in some instances. The possibility that alcohol or malnutrition suppresses or limits erythropoiesis was in no way evaluated in the present study.

The essentials of the present study can be stated quite concisely. The most significant abnormality of erythrocyte dynamics found in chronic, uncomplicated disease of the liver was a shortening of the actual mean red cell life due to various degrees of both an increased rate of cell aging and destruction of cells unrelated to age. In almost all the patients erythropoiesis increased to a degree sufficient to compensate for the increased cell loss. True anemia, or a subnormal red cell volume, was uncommon.

SUMMARY

1. Total red cell volume and radiochromium red cell survival were measured, and the red cell production was calculated, in a group of patients with chronic liver disease, chiefly cirrhosis.
2. Anemia as determined by the red cell volume was found in only three of twenty-nine patients. Patients with ascites or esophageal varices had the greatest red cell volumes.
3. The potential red cell life span was normal in six of twenty-one patients and slightly to moderately shortened in the remainder. Evidence of random cell destruction was present in all but one patient.
4. Normal or increased red cell production was found in all twenty patients. Only one of these failed to maintain a normal red cell volume.
5. Five patients, four with cirrhosis and one an alcoholic without cirrhosis, studied by radio-

iron methods were found to have normal or increased total and effective erythropoiesis.

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A Rapid Screening Test for Deficiency of Plasma Ceruloplasmin and Its Value in the Diagnosis of Wilson's Disease*

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WILSON'S disease is characterized by the hereditary deficiency of the plasma copper protein, ceruloplasmin, and by progressive and fatal hepatolenticular degeneration [1-3]. It is very unusual for signs and symptoms of the latter to become manifest before the age of seven or eight years although the hypoceruloplasminemia appears to be present from birth [4]. Because persistent marked deficiency of ceruloplasmin is rarely found, except in patients with Wilson's disease, it should be of clinical value to find asymptomatic infants with low plasma ceruloplasmin levels since Wilson's disease is likely to develop in these children. Our knowledge of the pathogenesis and treatment of the disease suggests that it may prove possible to delay or prevent the development of the illness in such children. The present paper describes a procedure for determining deficiency of ceruloplasmin which is sufficiently simple to be applicable as a screening test to detect these children, and which may also be of value in the diagnosis of Wilson's disease in older subjects.

MATERIALS AND METHODS

Basis of Method. Ceruloplasmin catalyzes the oxidation of certain polyamines including para-phenylenediamine (ppd) [5,6]. Since ceruloplasmin is the only constituent of plasma possessing such oxidase activity [6], this activity has been used as a measure of the concentration of ceruloplasmin in plasma or serum by several investigators [4-9]. Some of their procedures, and the spot test to be described, depend on the facts that the rate of oxidation of ppd is pro-

portional to the plasma concentration of ceruloplasmin, and that purple-blue compounds are formed as a result of this oxidation.

When measured either by oxidase activity, or by utilizing other specific characteristics of ceruloplasmin [1-3,6,10,11], plasma or serum from normal human subjects contains between about 18 to 35 mg. of ceruloplasmin per 100 ml. [4]. Although many clinical conditions are accompanied by an increase in this concentration [4-6,10,11], a concentration below 15 mg. per 100 ml. has been reported only in the neonatal period [12,13], in the nephrotic syndrome [10,11], in patients with Wilson's disease [1-4,10,11], and occasionally in unaffected relatives of these patients [14,15]. Our test was devised so as to distinguish serums or plasma containing less than 20 mg. of ceruloplasmin per 100 ml. from those containing more.

Materials. A 0.5 per cent solution of para-phenylenediamine dihydrochloride (Eastman Organic Chemical No. 207) is prepared in a sodium acetate buffer of pH 5.7, and 0.5 ionic strength. Strips measuring 2 by 15 cm., of Whatman No. 1 or Schleicher and Schull 2043A filter paper are briefly immersed in this solution, and then blotted between sheets of clean absorbent paper. The strips are dried in a current of nitrogen at about 50°C. They then appear slightly off-white, but should show no further darkening for at least three weeks when kept in an atmosphere of dry nitrogen at room temperature.

A standard serum, containing between 18 and 20 mg. of ceruloplasmin per 100 ml., is selected, or prepared by mixing several serums, on the basis of any quantitative method for determining ceruloplasmin.‡

‡ Prepared paper strips, capillary tubes, and standard serum for clinical testing may be obtained from the Ortho Research Foundation, Raritan, New Jersey.

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FIG. 1. Spot tests of serums from a normal subject and a patient with Wilson's disease, compared with a standard serum containing 20 mg. of ceruloplasmin per 100 ml.

For validation of the spot test, serums or plasmas of low and normal ceruloplasmin concentrations were needed. The obvious source of serums with low levels of ceruloplasmin was patients with Wilson's disease but too few such subjects were available. Therefore, advantage was taken of the fact, already mentioned, that plasma ceruloplasmin levels are almost as low in newborn infants as in some patients with Wilson's disease, consequently serums from umbilical cord blood samples were used. A quantitative analysis of ceruloplasmin was carried out in each of these serums. Plasmas with normal levels of ceruloplasmin were taken from healthy children, one to six years old, on the Pediatric Service of the Bronx Municipal Hospital Center.

Test Procedure. Plasma or serum may be used. The former is conveniently obtained without venipuncture by allowing blood from a skin puncture to fill a heparinized capillary tube (Aloe, No. 23922), and settling the cells by gravity or centrifugation. The portion of the tube containing cells is broken off and discarded. If serum from venous blood is used, it should be drawn into a capillary tube.

At each end of one of the dried paper strips about 10 microliters of standard serum are applied by touching an open end of the capillary tube to the paper. Between these spots of standard serum several unknown samples may be applied on the strip approximately 2 cm. apart.

The strip is placed in a test tube or flask containing a moist pledget of cotton which does not touch the paper. The container is stoppered and immersed in water at 45° to 55°C. for five to ten minutes. The intensity of the blue color developed by the unknown spots is compared to the blue color of the standard spots. The comparison should permit the determination of the ceruloplasmin concentration of each plasma or serum as greater or less than the standard. (Fig. 1.)

Statistical Methods. In order to determine whether or not the spot test is an acceptable procedure for screening serums with low concentrations of ceruloplasmin, its performance was investigated from the point of view of sensitivity, specificity and reproducibility using Wald's sequential method for the statistical analysis [76]. In describing the experiments which were performed the following definitions will be useful: A spot test is called negative if it indicates that the tested serum contains more ceruloplasmin than the

standard, and it is called positive if it indicates that the tested serum contains less ceruloplasmin than the standard.

The necessary spot tests were carried out in the following manner. The experimenter presented each sample to be tested in a capillary tube to two independently working observers. These observers did not know whether the capillary tube contained serum from cord blood or plasma from an older child, nor did they know the quantitative ceruloplasmin content of the samples. They prepared the spots and judged them to be negative or positive. Discordant results of the two observers, if encountered, were resolved by tossing a coin, a procedure equivalent, in the long run, to taking an average reading.

Three statistical hypotheses were formulated and tested. The first concerned the proportion of negative results of the spot tests in a group of serums each of which, by quantitative analysis, contained less than 16 mg. of ceruloplasmin per 100 ml. Clearly, a large proportion of negative test results among these serums would indicate that the spot test fails to detect a large proportion of just those subjects in whom Wilson's disease is likely to develop. Thus the higher this proportion, the less sensitive is the spot test. The statistical test was carried out sequentially with the following criteria: The null hypothesis that at least 15 per cent of the serums with low concentrations of ceruloplasmin (under 16 mg. per 100 ml., by quantitative measurement) appeared higher than 18 to 20 mg. per 100 ml. by the spot test was tested against the alternative hypothesis that this proportion was at most 5 per cent. The statistical risks adopted were as follows: If the null hypothesis were true, it would not be rejected more often than 5 per cent of the time. On the other hand, the null hypothesis would not be accepted more often than 5 per cent of the time if, in fact, the alternative were true.

The second statistical hypothesis concerned the proportion of positive results of the spot tests in the population to which the spot test is to be applied clinically. If this proportion is found to be low, the proportion of false positive test results must be even lower, and since Wilson's disease is rare, the specificity of the spot test will be high. The statistical procedure tested sequentially the null hypothesis that the proportion of positive results of the spot tests in the population from which the one to six year old

TABLE I
MEASUREMENT OF CERULOPLASMIN CONTENT OF SERUM
FROM CORD BLOOD BY QUANTITATIVE ENZYMATIC
ASSAY AND BY THE SPOT TEST

Infant	Ceruloplasmin (Quantitative)* (mg./100 ml.)	Ceruloplasmin by Spot Test†	Ceruloplasmin in Standard Serum (mg./100 ml.)
1	13	x	19
2	11	x	19
3	10	x	19
4	11	x	19
5	9	x	19
6	7	x	19
7	64	—	19
8	13	x	19
9	16	x	19
10	10	x	19
11	16	x	19
12	10	x	19
13	8	x	18
14	16	x	18
15	7	x	18
16	14	x	18
17	17	x	18
18	14	x	18
19	13	x	18
20	9	x	18
21	13	x	18
22	12	x	18
23	9	x	18
24	12	x	18
25	12	x	20
26	10	x	20
27	10	x	20
28	25	—	20
29	18	x	20
30	11	x	20
31	8	x	20
32	11	x	20
33	36	—	20
34	6	x	20
35	5	x	20
36	11	x	20
37	40	—	20

* By enzymatic method [4].

† x = less than standard.

— = greater than standard.

children were drawn at least 15 per cent against the alternative that it is at most 5 per cent with the same risks of erroneous decision as already mentioned.

The third statistical hypothesis concerned the frequency of disagreement in the results of two observers. The null hypothesis that the proportion of disagreements is at least 8 per cent was tested against the alternative that it is at most 3 per cent with the same statistical risks of error as before.

Obviously, rejection of each of these null hypotheses was the decision favorable to the spot test and, in fact, unless this decision had been reached in each case, the spot test would not have been acceptable.

RESULTS

The results were favorable to the spot test in all three experiments designed to test the hypotheses described. In the first experiment the null hypothesis was rejected, in accordance with the sequential plan, when no spot tests indicat-

ing serum containing more than 18 to 20 mg. per 100 ml. were found among twenty-seven serum samples with known low ceruloplasmin levels. The results of the spot test and quantitative determinations of ceruloplasmin on these twenty-seven serum specimens of cord blood (and on serums from ten additional infants) are given in Table I. It should be noted that the results of the spot test were also correct in each of the four instances in which the cord blood serum contained more than 18 to 20 mg. ceruloplasmin per 100 ml., presumably as a result of contamination with maternal blood containing a high concentration of ceruloplasmin [10,12,13].

In the second experiment the null hypothesis was rejected when no spot tests indicating serum containing less than 18 to 20 mg. of ceruloplasmin per 100 ml. were found in twenty-seven children aged one to six years.

The third experiment terminated when, in ninety-six pairs of observations, there were ninety-four in which both observers were in agreement. In the two instances in which there was disagreement quantitative enzymatic determination [4] showed that one serum contained 18 and the other 23 mg. of ceruloplasmin per 100 ml. Both of these were specimens from children in the second experiment, and in each case the coin toss designated the spot test as negative. Incidentally, the child with 18 mg. of ceruloplasmin per 100 ml. was found to be suffering from the nephrotic syndrome and had been included in this experiment by error.

Finally, serum from six children and adults with Wilson's disease were all shown, by the spot test, to contain less than 18 to 20 mg. of ceruloplasmin per 100 ml.

COMMENTS

We believe that the chief clinical value of this test will lie in screening apparently healthy children to detect those who are deficient in ceruloplasmin. Since Wilson's disease is an uncommon condition and practically the only cause of persistent deficiency of ceruloplasmin, usually in the range of 0 to 15 mg. per 100 ml. of serum, confirmatory studies, including quantitative analysis for ceruloplasmin, can be made in the relatively small number of children in whom positive results of the spot tests are obtained. In children who show persistent ceruloplasmin deficiency Wilson's disease is reasonably certain to develop [1-4,10], but early diagnosis may make it possible to prevent or delay the appear-

ance of clinical hepatolenticular degeneration. It appears that retention and deposition in the body of excessive amounts of copper are responsible for the pathologic changes, which are most clearly seen in the liver, brain, kidneys, eyes and nails [1-3, 17, 18]. Therefore, if latent Wilson's disease, or hypoceruloplasminemia, is demonstrated, measures may be instituted to minimize the absorption of copper from the diet, and to promote the excretion of copper already absorbed [19-24].

The neonatal deficiency of ceruloplasmin will not interfere with a screening program in children since it appears to be of short duration. In infants of apparently healthy mothers serum ceruloplasm concentrations appear to be persistently above 18 mg. per 100 ml. by the second month of life [25]. Therefore, it seems that the spot test can be used as a screening procedure in infants at any time after the age of three months, perhaps most conveniently at a time when routine immunizations are given.

Difficulty in interpretation of low concentrations of ceruloplasmin may occasionally arise. There is evidence that levels of ceruloplasmin may be low in patients with the nephrotic syndrome, and indirect evidence, from studies of plasma copper, that there may be a deficiency of this protein in patients with kwashiorkor, tropical sprue, and in certain infants with a syndrome of anemia and hypoproteinemia [10, 26-28]. Furthermore, as already pointed out, some asymptomatic relatives of patients with Wilson's disease may have plasma ceruloplasmin concentrations within the range found in the patients [14, 15]. These four disease states should be readily differentiable from asymptomatic Wilson's disease, but careful and continued observation of other subjects with hypoceruloplasminemia, together with investigation of their families, may be necessary as aids in determining whether or not Wilson's disease is likely to develop in the patient. It may be pointed out that clear signs and symptoms of Wilson's disease occasionally first appear as late as the third and fourth decade.

The spot test may also be of value in the clinical study of patients suspected of having Wilson's disease, such as subjects with unexplained hepatic cirrhosis [29, 30] or neurologic symptoms consistent with Wilson's disease. It should be pointed out that in some patients with overt Wilson's disease the usually low level of ceruloplasmin may be temporarily elevated by

the administration of estrogens [2, 31] and, perhaps, by the same intercurrent clinical conditions which increase the concentration of this protein in subjects without Wilson's disease [10, 11]. Furthermore, at least one patient is known to have died of this disease despite the presence of an undoubtedly normal concentration of ceruloplasmin, and the absence of any relevant intercurrent condition [32]. These facts should be borne in mind in interpreting the results of the spot test, particularly when a negative test result is found in any patient in whom there is a strong suspicion of Wilson's disease.

SUMMARY

A spot test is described which makes it possible to determine simply and with a satisfactory degree of certainty whether or not an individual has more or less than about 20 mg. of ceruloplasmin per 100 ml. of plasma or serum. The test should be applicable as a screening procedure to detect asymptomatic children with hypoceruloplasminemia in whom Wilson's disease may subsequently develop. Based on current knowledge, and with available pharmacologic agents, it may be practicable to prevent or delay the onset of symptoms and signs of Wilson's disease in such children. The test may also be used in the study of patients suspected of having Wilson's disease.

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Studies on Copper Metabolism XXIX

*A Critical Analysis of Serum Copper and Ceruloplasmin Concentrations in Normal Subjects, Patients with Wilson's Disease and Relatives of Patients with Wilson's Disease**

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THE original observation [1] that Wilson's disease is associated with a deficiency of the serum copper protein, ceruloplasmin, has been confirmed by immunologic measurement of ceruloplasmin [2] and by serum oxidase measurements [2-6]. Since the disorder is inherited [4,7], the suggestion has been made that the fundamental effect of the abnormal gene, when present in the homozygous form, is to cause inadequate synthesis of ceruloplasmin [1,4,7-9]. According to this theory, the increased absorption of copper from the gastrointestinal tract, the excessive deposition of copper in tissues and the increase in non-ceruloplasmin copper in the serum are secondary to the deficiency of ceruloplasmin.

If this concept is correct in its simplest form, which would be to assume that there are no environmental factors or gene to gene interactions which influence the expression of the abnormal gene, it follows that: (1) a deficiency of ceruloplasmin should exist in all patients with the disease; (2) a correlation between the concentration of ceruloplasmin present and the duration and severity of the disease may be present; (3) a decreased concentration of ceruloplasmin might not be observed in chronic disorders other than Wilson's disease; and (4) all reversible manifestations of the disorder should be alleviated by restoration of the ceruloplasmin concentration to the normal level for an appropriate period of time.

Although no extensive analysis of this concept has been reported, a few scattered observations have been made which tend to cast doubt on its validity [2,9]. Normal serum copper values have been observed in a few patients with Wilson's disease [2,3]. This, of course, does not eliminate the possibility that the concentration of ceruloplasmin might have been low in the reported cases because it is known that the "direct-reacting" fraction of serum copper is usually increased in this disorder [8]. In several patients, however, the ceruloplasmin concentration [2] and serum oxidase activity [3] have been noted to be only slightly below the limits of normal. In a small series of fourteen patients with this disease we were unable to observe a correlation between the ceruloplasmin concentration and the duration or severity of the disease [2]. Ceruloplasmin concentrations as low as those observed in Wilson's disease have been found in three patients with the nephrotic syndrome [2] and in two infants with idiopathic hypocupremia [10]. Finally, abnormally low total serum copper concentrations have been observed in normal, asymptomatic relatives of patients with Wilson's disease [5,6,11-14]. A number of these relatives have been beyond the age at which Wilson's disease is usually manifest.

The purposes of this paper are: (1) to present a critical analysis of the serum copper and ceruloplasmin concentrations in normal human subjects, patients with Wilson's disease and rela-

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† Postdoctoral Fellow of the American Cancer Society.

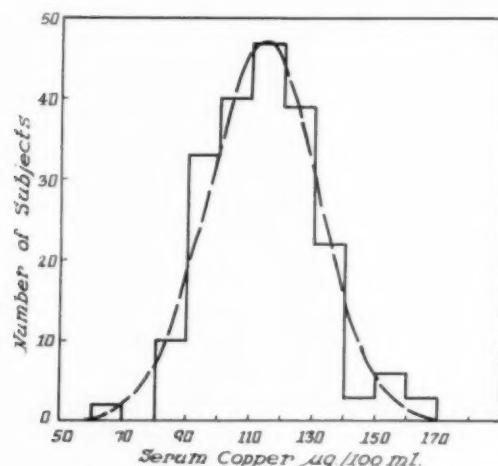


FIG. 1. Distribution curve for total serum copper in 205 normal subjects. The broken line is a normal distribution curve which has been fitted to the sample distribution.

tives of patients with Wilson's disease; and (2) to examine the possible role of ceruloplasmin in the pathogenesis of this rare inherited disorder.

MATERIALS AND METHODS

The control group of 205 subjects ranged in age from seventeen to forty-five years and consisted of normal medical students, physicians and laboratory personnel.*

Serums from thirty-six patients with Wilson's disease have been studied. Six of these (Cases 1, 3, 5, 14, 15 and 27) were patients in our own clinic. The remaining serums were provided by physicians elsewhere. All thirty-six of the patients had Kayser-Fleischer rings and one or more signs of liver disease.

The methods for the determination of total serum copper and urine copper have been published elsewhere [15,16]. Ceruloplasmin was measured immunologically by the use of rabbit antihuman ceruloplasmin serum which had been absorbed with serum from a patient with Wilson's disease [7,2].

The methods outlined by Croxton [17] for the statistical analysis of data have been followed. In the text, S.D. refers to standard deviation; S.E. refers to the standard error of the mean; r refers to the correlation coefficient; and P refers to the probability that such an event could occur by chance. Only P values of 0.01 or less have been considered to be significant.

RESULTS

Normal Subjects. The serum copper values obtained in 205 normal subjects are summarized in Table I. The difference between the means of

* In a previous publication [2] we stated that total serum copper had been measured in 228 normal subjects. On reinspection of the data it has been discovered that twenty-three of the subjects had been included twice.

TABLE I
NORMAL SERUM COPPER VALUES

Group	No.	Mean \pm S.D. ($\mu\text{g}/100 \text{ ml}$)	Range ($\mu\text{g}/100 \text{ ml}$)
Male	120	110 \pm 15.7	68 to 161
Female	85	120 \pm 17.8	83 to 165
Total	205	114 \pm 17.4	68 to 165

the sexes is highly significant ($P = <0.001$). The distribution curve for the values obtained in the group of 205 subjects is shown in Figure 1 together with a normal distribution curve which has been fitted to the sample distribution. The experimental values fit the normal curve within the limits of variation due to random sampling ($P = >0.30$).

Values greater than 2 standard deviations below the normal mean ($70 \mu\text{g}/100 \text{ ml}$) were obtained in two male subjects. In both subjects the value obtained was $68 \mu\text{g}/100 \text{ ml}$. As shown in Figure 1, these values fall within the normal distribution curve and therefore must be considered normal. The values have been reasonably reproducible in one of the subjects over an eight-year period. (Table II.) The other subject, when studied eight years after the initial observation, was found to have a serum copper value of $92 \mu\text{g}/100 \text{ ml}$. Both of these subjects (ages thirty-two and thirty, respectively) are physicians, neither has any stigmas of Wilson's disease and in neither family has there been a history of

TABLE II
TWO NORMAL MALE SUBJECTS WITH LOW SERUM COPPER VALUES

Year	Serum Copper ($\mu\text{g}/100 \text{ ml}$)	Ceruloplasmin ($\text{mg}/100 \text{ ml}$)
<i>Subject A</i>		
1951	68	..
1954	68	..
1955	69	20
1958	85	14
1959	71	15
<i>Subject B</i>		
1951	68	..
1959	92	22

the occurrence of this disease. The excretion of copper in the urine of subject A has been studied and has been found to be within normal limits.

Ceruloplasmin determinations have been performed in ten normal subjects [2]. The mean value ± 1 S.D. was 34 ± 4.0 mg./100 ml., with a range from 27 to 38 mg./100 ml. The mean value for serum copper in these ten specimens was 108 $\mu\text{g}./100$ ml., with a range of 92 to 123 $\mu\text{g}./100$ ml. Since the normal serum copper, defined as ± 2 S.D. in the considerably larger group of normal subjects is 79 to 149 $\mu\text{g}./100$ ml., the values cited for ceruloplasmin may not represent the true range. However, there is a high degree of correlation between the indirect-reacting (total minus direct-reacting fraction) serum copper fraction and ceruloplasmin in normal subjects [2]. The direct-reacting fraction normally accounts for about 6 per cent of the total serum copper. Therefore, in normal subjects ceruloplasmin can be calculated from the total serum copper by use of the following formula:

$$\begin{aligned} \text{Ceruloplasmin (mg./100 ml.)} \\ = \frac{\text{Serum copper } (\mu\text{g./100 ml.}) \times 0.94}{3.2} \end{aligned}$$

If this formula is used, the range for ceruloplasmin in normal subjects, defined as ± 2 S.D., becomes 23 to 44 mg./100 ml. The determined values for ceruloplasmin in the two normal subjects with low serum copper values were below this level, namely from 14 to 22 mg./100 ml. (Table II.)

Wilson's Disease. Data on thirty-six patients with Wilson's disease are summarized in Table III. Statistical comparisons of subgroups are presented in Table IV.

The mean age for the group, at the time the studies were made, was twenty-three years with a range of nine to thirty-five years. There were twenty-one males and fifteen females, a ratio of males to females of 1.4:1. The duration of symptoms at the time of the studies ranged from zero to twenty-one years. Three patients were asymptomatic siblings of patients with the disorder. Eight of thirty-six patients had no clinical signs or symptoms of neurologic disease. The remaining twenty-eight patients showed tremor, dysarthria or spasticity. The patients with neurologic disease had had symptoms for a distinctly longer period of time than those who showed no signs of neurologic disease. (Table IV.)

TABLE III
WILSON'S DISEASE

Case No.	Age (yr.)	Sex	Duration Symptoms (mo.)	Neuro-logic Involvement	Serum Copper ($\mu\text{g./100 ml.}$)	Cerulo-plasmin (mg./100 ml.)
1	18	M	24	+	57	2
2	27	M	120	+	34	3
3	19	M	18	+	63	3
4	13	F	24	+	42	4
5	35	M	144	+	50	4
6	23	M	48	+	43	4
7	14	M	48	+	39	5
8	9	F	1	-	99	6
9	23	F	36	+	23	6
10	31	M	60	+	52	6
11	29	M	60	-	54	7
12	26	M	36	+	38	7
13	29	M	36	+	52	8
14	11	F	0	-	53	8
15	15	M	72	+	35	9
16	17	M	72	-	46	9
17	22	M	156	+	60	10
18	30	F	48	+	53	10
19	15	F	1	-	72	10
20	35	F	252	+	72	11
21	31	F	1	+	60	11
22	20	M	96	+	72	12
23	24	F	18	+	81	14
24	25	M	18	+	69	15
25	19	M	0	-	100	17
26	23	M	0	-	90	17
27	29	F	36	+	86	19
28	14	M	24	-	116	22
29	20	M	24	+	47	..
30	19	F	36	+	52	..
31	34	F	96	+	90	..
32	34	F	84	+	72	..
33	18	F	108	+	72	..
34	16	F	24	+	54	..
35	35	M	240	+	50	..
36	24	M	48	+	50	..

Copper was measured in the serums of all thirty-six patients. The mean value ± 1 S.D. for the group was 61 ± 20.8 $\mu\text{g./100 ml.}$ This value was significantly different from the normal mean ($P = <0.001$). In twenty-nine patients (80 per cent) the values were less than 79 $\mu\text{g./100 ml.}$ In seven patients (20 per cent) the values were within 2 S.D. of the normal mean. The values in the male patients did not differ from the values in the females. No correlation was observed between the total serum copper values and age ($r = -0.2$; $P = >0.20$).

Ceruloplasmin was determined in the serums of twenty-eight of the thirty-six patients. The mean value ± 1 S.D. for the group was 9 ± 5.2 mg./100 ml. This value was significantly different from the normal mean ($P = <0.001$). In all twenty-eight patients the value was less than 23 mg./100 ml. The values in the male patients did not differ from the values in the female patients. No correlation was observed

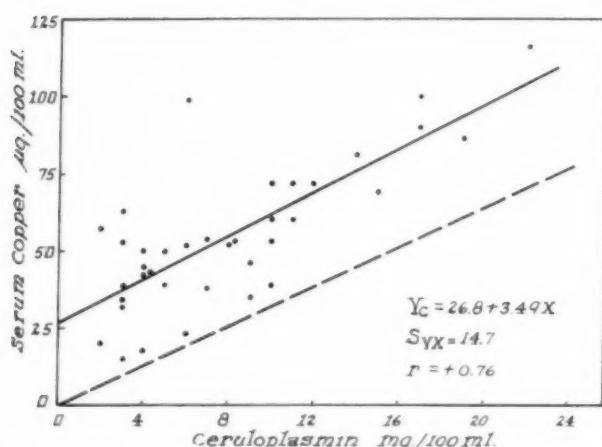


FIG. 2. Correlation between total serum copper and ceruloplasmin in twenty-eight patients with Wilson's disease. The solid line is placed through the experimental data. The estimating equation was computed by the method of least squares. S_{YX} refers to the standard error of estimate. The broken line represents the amount of copper contributed by ceruloplasmin, assuming a concentration of copper in ceruloplasmin of 0.32 per cent.

between the ceruloplasmin values and age ($r = +0.03$; $P = >0.80$).

A high degree of correlation was observed between the serum copper values and ceruloplasmin concentrations ($r = +0.76$; $P = <0.001$). (Fig. 2.) The broken line in Figure 2 represents the amount of copper contributed by ceruloplasmin, assuming a concentration of copper in ceruloplasmin of 0.32 per cent. The vertical

distance between the broken line and any given experimental point represents the amount of copper contributed by the direct-reacting, non-ceruloplasmin copper. As already stated, in normal subjects this fraction represents about 6 per cent (0 to 21 $\mu\text{g}/100 \text{ ml}$) of the total copper present [2,8]. Thus, in confirmation of earlier studies [8], it is apparent that the direct-reacting fraction is greatly increased in this disorder. Furthermore, the ratio of direct-reacting copper to total copper increases as the ceruloplasmin decreases. In one patient the serum copper value (99 $\mu\text{g}/100 \text{ ml}$) was disproportionately great for the ceruloplasmin concentration of 6 mg./100 ml. In this patient, however, it is entirely possible that the serum specimen was contaminated by extraneous copper.

To ascertain whether or not a relationship between the serum copper or ceruloplasmin values and the duration of the clinical manifestations did exist, the data were evaluated in several ways. When the serum copper values were plotted against the duration of symptoms in all the cases, no correlation was observed ($r = -0.15$; $P = >0.30$). A similar situation prevailed for ceruloplasmin ($r = -0.16$; $P = >0.40$). On the other hand, comparison of the serum copper levels in six patients with no symptoms, or with symptoms of less than twelve months' duration, with the values in nine pa-

TABLE IV
WILSON'S DISEASE
STATISTICAL COMPARISONS OF SUBGROUPS

Group or Subgroup	Total Serum Copper			Ceruloplasmin		
	No.	Mean \pm S.E. ($\mu\text{g}/100 \text{ ml}$)	P*	No.	Mean \pm S.E. (mg./100 ml.)	P*
Total group.....	36	61 \pm 3.47		28	9 \pm 1.00	
Male.....	21	58 \pm 4.67	>0.30	18	9 \pm 1.34	
Female.....	15	65 \pm 5.13		10	10 \pm 1.39	>0.60
Subjects with neurologic signs.....	28	57 \pm 3.03		20	8 \pm 1.03	
Subjects with no neurologic signs.....	8	79 \pm 9.23	0.05	8	12 \pm 2.08	>0.10
Duration of symptoms						
Subjects with neurologic signs.....				28	70 \pm 11.8†	
Subjects with no neurologic signs.....				8	20 \pm 10.5†	0.005

* P indicates the probability that such an event could occur by chance.

† Number of months.

TABLE V*
COMPARISON OF DURATION OF SYMPTOMS WITH SERUM
COPPER AND CERULOPLASMIN VALUES IN
WILSON'S DISEASE

Groups	No.	Serum Copper ($\mu\text{g}/100 \text{ ml}$)	Ceruloplasmin ($\text{mg}/100 \text{ ml}$)
Symptoms < 12 months.....	6	79 ± 20.2	11.5 ± 4.6
Symptoms > 60 months.....	9	53 ± 13.8	7.9 ± 3.1
Probability of event occurring by chance.....	..	0.01	>0.05

* Figures refer to mean ± one S.D.

tients with the disease for sixty months or more did reveal a significant difference. (Table v.) A similar difference was not obtained between the ceruloplasmin values and the duration of symptoms. Serum copper and ceruloplasmin values were obtained over a period of one or more years in three patients. (Table vi.) In two there seemed to be a decrease in both copper and ceruloplasmin with time; in the third patient no such trend was apparent.

The clinical severity of the disease is a difficult parameter to measure quantitatively. However, the presence or absence of neurological signs and symptoms perhaps may be taken as one criterion of the severity of the disease. Using this criterion only a questionable relation between the severity of the disease and serum copper levels could be shown. (Table iv.) No significant difference between the levels of ceruloplasmin in subjects with and without neurologic manifestations was observed. Another criterion which might be considered is the general clinical condition of the patient and the course of the illness. In this regard the course of one patient (No. 1) is of interest. He had been clinically well except for slight dysarthria and tremor, and had worked full time as a house painter from November 30, 1954 to February 14, 1957. The serum copper values ranged from 33 to 69 $\mu\text{g}/100 \text{ ml}$. and the ceruloplasmin values from 2 to 5 $\text{mg}/100 \text{ ml}$. during this period. On January 3, 1957, he was given 1 mg. of ethinyl estradiol daily orally [7,18]. On the nineteenth day of therapy the ceruloplasmin level had increased progressively to 10 $\text{mg}/100 \text{ ml}$. but his general condition had deteriorated markedly. From February 16, 1957 to May 31, 1957 he was comatose, being unable to walk, eat, understand or communicate. In this interval the serum copper values ranged from 8 to 40 $\mu\text{g}/100 \text{ ml}$. and ceruloplasmin values were between 2 and 4 $\text{mg}/100 \text{ ml}$.

TABLE VI
SERUM COPPER AND CERULOPLASMIN CHANGES
DURING THE COURSE OF WILSON'S DISEASE

Date	Serum Copper ($\mu\text{g}/100 \text{ ml}$)	Ceruloplasmin ($\text{mg}/100 \text{ ml}$)
<i>Patient 1</i>		
11/30/54	57	2
7/8/55	33	3
1/7/56	39	3
1/3/57	50	5
6/10/57	20	2
1/24/59	29	3
<i>Patient 14</i>		
6/7/54	53	8
1/7/56	53	3
8/13/57	45	4
6/12/58	15	3
1/12/59	29	1
<i>Patient 27</i>		
5/22/54	86	19
8/24/55	39	9

Following institution of penicillamine therapy he made a rapid recovery and since then he has been fully and gainfully employed in his occupation, with serum copper values between 16 and 55 $\mu\text{g}/100 \text{ ml}$. and ceruloplasmin levels of 2 to 3 $\text{mg}/100 \text{ ml}$. Thus in this person there seemed to be little correlation between his general condition and the concentrations of serum copper or ceruloplasmin. Again, another patient (No. 14) has been participating in school activities for three years although the ceruloplasmin level was only 3 to 4 $\text{mg}/100 \text{ ml}$. On the other hand, one patient (No. 27) died of the disease with a ceruloplasmin concentration of 9 $\text{mg}/100 \text{ ml}$. and another (No. 28) died about two months after a ceruloplasmin level of 22 $\text{mg}/100 \text{ ml}$. was found.

An opportunity occurred to observe the influence of a normal pregnancy on the serum copper and ceruloplasmin values of one patient. (Table iii, No. 9.) The results are shown in Table vii. During the pregnancy there was an appreciable increase in ceruloplasmin, with a maximum value on the day of delivery. The values declined rapidly in the postpartum period. Analysis of the placental vein blood at

TABLE VII
INFLUENCE OF NORMAL PREGNANCY ON SERUM COPPER
AND CERULOPLASMIN OF A PATIENT WITH WILSON'S
DISEASE

Date	Serum Copper ($\mu\text{g}/100 \text{ ml}$)	Ceruloplasmin ($\text{mg}/100 \text{ ml}$)
7/6/56	51	11
7/9/56	54	11
8/8/56*	105	18
8/22/56	93	8
3/14/57	23	6

* Day of delivery.

the time of delivery revealed a serum copper level of $93 \mu\text{g}/100 \text{ ml}$. and a ceruloplasmin concentration of $1.5 \text{ mg}/100 \text{ ml}$. [9]. Serum, obtained from the infant at seven months of age, contained $94 \mu\text{g}/100 \text{ ml}$. of total copper and $26 \text{ mg}/100 \text{ ml}$. of ceruloplasmin.

Relatives of Patients with Wilson's Disease. Abnormally low values for ceruloplasmin, obtained in eight of twenty-one relatives of patients with Wilson's disease, are presented in Table VIII. None of these subjects had any symptoms or signs of the disease. Liver function studies were performed in all but two subjects (E and F) and in all the values obtained were within normal limits. The urinary excretion of copper was measured in five subjects (A, B, C, D and G). In each case the excretion of copper was within normal limits. Two subjects (A and E) are well beyond the age when the clinical manifestations of the disease usually first appear. Whether the disease will develop in any of the younger relatives listed in Table VIII remains to be determined. However, it is apparent from subjects A and E that low ceruloplasmin levels are not always accompanied by the clinical manifestations of Wilson's disease.

Subject A was studied one year after the initial observation. The second observations were $108 \mu\text{g}/100 \text{ ml}$. and $20 \text{ mg}/100 \text{ ml}$. respectively. Subject B was studied for a second time two years after the initial observation. The new findings were $60 \mu\text{g}/100 \text{ ml}$. and $21 \text{ mg}/100 \text{ ml}$. for serum copper and ceruloplasmin, respectively.

It should be noted that low ceruloplasmin values were obtained in three subjects (A, C and D) in the presence of normal amounts of total serum copper. These subjects apparently had increased amounts of direct-reacting serum

TABLE VIII
SERUM COPPER AND CERULOPLASMIN VALUES IN SELECTED
RELATIVES OF PATIENTS WITH WILSON'S DISEASE

Proprietary Case No.	Subj- ject No.	Relationship	Age (yr.)	Serum Copper ($\mu\text{g}/100 \text{ ml}$)	Cerulo- plasmin ($\text{mg}/100 \text{ ml}$)
1	A	Father	62	93	20
	B	Brother	25	75	22
	C	Brother	16	109	20
	D	Sister	9	143	23
14, 15	E	Grandmother	65	65	19
	F	Uncle	32	64	19
16	G	Cousin (male)	14	77	16
None	H	Brother	17	66	16

copper. It is also interesting that six of the eight subjects were males. Neale and Fischer-Williams [12] likewise observed hypocupremia more frequently in male than female relatives.

The mother of patient A had normal serum copper and ceruloplasmin values. Both parents of siblings 14 and 15 had normal serum copper and ceruloplasmin values. Therefore, a low ceruloplasmin concentration is not an invariable characteristic of the heterozygous condition.

COMMENTS

From the data presented it is apparent that Wilson's disease is accompanied by a decrease in the ceruloplasmin concentration in the serum. This was a consistent observation, without exception, in twenty-eight patients so studied. However, for a number of reasons it seems clear that the fundamental defect is not simply or solely represented by a decrease in the ceruloplasmin concentration.

(1) All patients with Wilson's disease had ceruloplasmin values which were less than the normal mean -2 S.D . Nevertheless, the values (14 to $22 \text{ mg}/100 \text{ ml}$) in six patients were as great as the values observed in two normal subjects. (Table II.)

(2) Within the group of patients studied, there was a poor correlation between the ceruloplasmin level and the duration and severity of the manifestations. A patient with a rather fulminating form of the disease had a ceruloplasmin level of $22 \text{ mg}/100 \text{ ml}$. several months prior to death. Two patients who have been followed up for periods of three to five years have had ceruloplasmin concentrations below $4 \text{ mg}/100 \text{ ml}$. and yet have been able to carry on daily in normal physical activities. Finally, even though therapy with sodium sulfide, BAL

or penicillamine is occasionally associated with a dramatic improvement in the condition of the patient, such improvement following therapy has not been associated with an increase in serum copper or ceruloplasmin values [19].

(3) If a deficiency of ceruloplasmin directly or indirectly produces the lesions characteristic of Wilson's disease, then a deficiency of ceruloplasmin from whatever cause should be associated with the lesions of Wilson's disease. In addition to the two normal subjects mentioned, ceruloplasmin levels as low as those observed in Wilson's disease have been observed in a few patients with the nephrotic syndrome [2], in newborn infants [9], and in infants with idiopathic hypocupremia [10]. Serum copper levels as low as those observed in hepatolenticular degeneration have been found in some patients with sprue [20,21]. None of these patients have shown the clinical manifestations or other biochemical abnormalities of Wilson's disease. It may be argued, of course, that the deficiency of ceruloplasmin in these other conditions is of relatively brief duration and that the deficiency must persist for a period of five years or more before the manifestations of Wilson's disease become evident. However, ceruloplasmin levels of 16 to 23 mg./100 ml. have been observed in eight relatives of patients with the disease. Although we cannot state that these levels have been present for the lifetime of the subjects, observations repeated one and two years later in two of the adult subjects again were low. The two normal subjects studied with ceruloplasmin values between 14 and 22 mg./100 ml. probably have maintained these levels over at least an eight-year period.

(4) If a deficiency of ceruloplasmin were the primary defect in this condition, it follows that restoration of the ceruloplasmin level to normal should result in alleviation of all reversible manifestations of the disease. This hypothesis has not had an adequate experimental test since ceruloplasmin levels have not been increased to normal values and maintained within normal limits for long periods of time. Nevertheless, it can be pointed out that an increase in ceruloplasmin concentration in a single patient given ethinyl estradiol, and in one patient in whom the ceruloplasmin concentration increased during normal pregnancy, was not associated with noticeable improvement in the clinical condition of either patient. Bearn [7] has noted an increase in serum copper to normal or supernormal

levels in three patients with Wilson's disease treated with estrogen. The increase in serum copper was not accompanied by an increase in the urinary excretion of copper or noticeable clinical improvement. Bickel et al. [22] attempted prolonged substitution therapy with ceruloplasmin in several patients with Wilson's disease but, due to side reactions of the therapy and other complications, the results were inconclusive.

These observations, taken together, strongly suggest that a deficiency of ceruloplasmin is not the single uncomplicated determinant of the disease. The evidence for this statement is at least sufficiently good to encourage investigators to look for environmental factors or gene to gene interactions which influence the expression of the abnormal gene for ceruloplasmin synthesis, if such an abnormal gene exists at all. At the present time no such factors or interactions are recognized. Another possibility is that the ceruloplasmin present in the serum of patients with Wilson's disease, in addition to being quantitatively decreased, is not functionally normal. This possibility has not been entirely eliminated although there are two reasons to deny it. The oxidase activity per unit of ceruloplasmin is the same in Wilson's disease as in normal subjects [2-6]. Uriel et al. [23] have examined certain immunochemical characteristics of ceruloplasmin from normal subjects and from patients with Wilson's disease, and they have been unable to establish any differences. Finally, the possibility must be considered that the deficiency of ceruloplasmin in Wilson's disease is only a secondary manifestation and is not fundamentally involved in the inheritance or the pathogenesis of the disorder. Histological alterations in the liver are an invariable finding in patients dying of this disease. It is possible that diminished ceruloplasmin synthesis is secondary to a specific metabolic abnormality of the liver which is itself the fundamental inherited defect. This possibility has been suggested by Uzman et al. [24-26] and some experimental data to support this view have been presented.

A few general comments may be made concerning the diagnosis of Wilson's disease. Hypocupremia is not invariably present in this disorder. In an occasional patient with the disease the ceruloplasmin concentration may not be lower than that which can be found in a few normal subjects. When present, hypocupremia

and hypoceruloplasminemia are not specific for Wilson's disease. Indeed, normal relatives of patients with this disease may have these two biochemical abnormalities. In those relatives with low ceruloplasmin levels in whom urinary copper excretion has been studied, hypercupriuria has not been observed [6,11-13]. Hypercupriuria is usually, if not always, present in patients with Wilson's disease [3,8]. However, hypercupriuria has been observed in conditions other than Wilson's disease, particularly in patients with hepatic disorders [3,16] and in patients with the nephrotic syndrome [27]. On the other hand, Kayser-Fleischer rings have not been described in any condition other than Wilson's disease, and all thirty-six patients with the disease whom we have investigated have had readily identifiable Kayser-Fleischer rings. As pointed out by Warnock and Neill [13], since the metabolic changes in Wilson's disease have become known, there has not been an authentic example of the disease reported without Kayser-Fleischer rings.

In a previous publication [2] we listed one patient (P. C.) without Kayser-Fleischer rings as a patient with Wilson's disease. The diagnosis was erroneously based on the presence of hypocupremia and hypoceruloplasminemia and the presence of bizarre neurologic manifestations associated with epilepsy. This subject is the cousin of a patient with Wilson's disease and he has subsequently been studied in detail and described elsewhere [13]. He is now completely asymptomatic, with none of the clinical manifestations of Wilson's disease [28]. In the present publication he is included with relatives in Table VIII (subject G). Therefore it is concluded that the most reliable diagnostic feature of the disease is the presence of the characteristic corneal rings. In our own experience, the corneal rings have always been present, even prior to the development of symptoms. The biochemical abnormalities, at best, can only confirm the diagnosis.

SUMMARY

1. Total copper and ceruloplasmin concentrations have been determined in the serums of normal subjects, patients with Wilson's disease and relatives of patients with Wilson's disease.
2. Total serum copper was determined in 205 normal subjects. The mean value ± 1 standard deviation (S.D.) was $114 \pm 17.4 \mu\text{g}/100 \text{ ml}$. In two subjects the values were $68 \mu\text{g}/100 \text{ ml}$.

The mean value ± 1 S.D. in thirty-six patients with Wilson's disease was $61 \pm 20.8 \mu\text{g}/100 \text{ ml}$. In seven patients the values were within 2 S.D. of the normal mean. Five normal relatives of patients with Wilson's disease were found to have serum copper values below $79 \mu\text{g}/100 \text{ ml}$.

3. Calculation of ceruloplasmin values from the 205 normal serum copper values gave a normal range, defined as ± 2 S.D., of 23 to 44 mg./100 ml. Ceruloplasmin was measured immunologically in ten normal subjects. The mean value ± 1 S.D. was $34 \pm 4.0 \text{ mg}/100 \text{ ml}$. The immunologically determined values for ceruloplasmin in the two normal subjects with low serum copper values were 14 to 22 mg./100 ml. By the same method the mean value ± 1 S.D. in twenty-eight patients with Wilson's disease was $9 \pm 5.2 \text{ mg}/100 \text{ ml}$. In all twenty-eight patients the value was less than 23 mg./100 ml. Ceruloplasmin values between 19 and 23 mg./100 ml. were observed in eight normal relatives of patients with Wilson's disease.

4. Within the group of patients studied there was poor correlation between the ceruloplasmin concentration and the duration and severity of the clinical manifestations.

5. It is suggested that a decreased concentration of ceruloplasmin is not the single uncomplicated determinant of the disease.

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Reviews

The Closing Mechanism at the Gastroesophageal Junction*

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THE nature of the closing mechanism at the gastroesophageal junction has been a matter of dispute since the eighteenth century [1]. Controversy exists concerning both the experimental observations and their interpretation. Even such apparently simple points as the presence or absence of an anatomic sphincter, or of a flap valve at the gastroesophageal junction, or the presence or absence of a pinchcock action of the diaphragm has been confirmed by some and denied by others.

There is general agreement that a closing mechanism must exist. This is immediately apparent from an appreciation of the fact that there is a negative pleuroperitoneal and esophagogastric pressure gradient. The intraluminal pressure of the stomach is from 10 to 25 mm. Hg higher than in the esophagus on inspiration, and on maximal inspiratory effort against the closed glottis, the pressure differential may rise to as high as 80 mm. Hg [2,3]. If there were no mechanism to close the lumen between these two cavities, reflux of gastric contents into the esophagus would result whenever favored by gravity.

A sphincter at the cardia was described by Helvetius [4] in 1719. Contraction and relaxation of this sphincter could account for the unidirectional passage of food and fluids from the esophagus into the stomach and would, at the

same time, constitute a barrier against gastroesophageal reflux. Subsequent studies, however, revealed that there was little documented evidence in support of an anatomic sphincter and other explanations were sought. The oblique entrance of the esophagus into the stomach combined with the sharp angle formed by the left wall of the abdominal esophagus and the right side of the gastric fundus were considered to constitute a flap valve which permitted the easy passage of food and liquids into the stomach. This valve was considered capable of preventing reflux [5,6]. A valve-like mechanism was also postulated based upon the behavior of the gastric mucosal folds about the cardiac orifice have the aspect of a rosette which could assist in preventing retrograde flow into the esophagus [7].

Extrinsic factors have also been considered to have an essential role in the closing mechanism. The diaphragm, the diaphragmatic-esophageal membrane, and the liver tunnel could help maintain the normal anatomic relationships which are necessary for normal functioning of the closing mechanism. It has been suggested that the bundles of muscle surrounding the diaphragmatic hiatus participate actively by pinching the esophagus shut by lateral compression, the so-called "pinchcock" action [8]. Finally, more recent physiologic studies have led to the concept

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of a physiologic sphincter which extends normally from 1 to 2 cm. above and 1 to 2 cm. below the diaphragm [9-12].

The purpose of the present report is to examine these theories and their experimental support, to discuss the interpretation of these observations, and to suggest other and perhaps more tenable working hypotheses.

THE ANATOMIC SPHINCTER

The question of the presence or absence of an anatomic sphincter in the gastroesophageal junction would seem easy to resolve. However, literature on this point is very confused. Many authors who have expressed their opinion on this problem detail a long list of investigators who are for or against the existence of an anatomic sphincter. The only evidence given by many is the mere statement that they believe or do not believe in it.

According to Lendrum [13], the anatomic sphincter is characterized by a distinct ring of circular muscles separated from the adjoining muscles by connective tissue septums. A dilator muscle, formed by longitudinal fibers, should be present and the thickened circular muscle should persist after the factor of spasm has been eliminated. Although rings of contraction and muscle thickening are frequently found at multiple sites along the gastrointestinal tract when cadavers are embalmed soon after death, these changes are not present during life.

Based upon the anatomic studies of several investigators [13-27], the following description of the muscle layers at the gastroesophageal junction may be given. The longitudinal or superficial muscle layer of the esophagus passes through the gastroesophageal junction without causing a thickening at the cardia and without dipping into the circular layer. The circular, or internal, muscle layer of the esophagus also continues down to the stomach where it becomes the mid-layer, which encircles the entire organ. The oblique fibers from the stomach form a U-shaped band that borders the cardiac incisura and extends downward, one arm located on the anterior and the other on the posterior surface of the stomach. These oblique fibers blend with the circular layer of the cardia.

The majority of anatomists deny the existence of a definite muscular ring, resembling a sphincter muscle [13,17,19,23,25,26]. Several authors describe a slight thickening of the circular muscle layers of the lower esophagus. Conflicting

opinions are expressed as to the exact localization of this discrete muscle band. Some [14,16,20] would locate it at the gastroesophageal junction. Others [22] consider it to extend over a distance of 1 to 1½ inches, or even higher, to involve the whole lower third of the esophagus. Lerche [24] described two circular bands, one at the cardia and one about 1 cm. above the diaphragm.

In summary, it is apparent that an anatomic sphincter, as defined by Lendrum [13], does not really exist at the cardia. What has been termed a sphincter represents either a slight thickening of the circular layer of the esophagus or the oblique fibers of the stomach, none of which have the characteristics of a true anatomic sphincter.

THE FLAP VALVE MECHANISM

A flap valve, closing off the cardiac orifice, was postulated by Braune [5] and von Gubaroff [6] as a result of their experiments on cadavers. They infused water through the esophagus, or through the duodenum into the stomach, after removing the upper portion of the trunk. The water returned through the esophagus only after large quantities had been forced into the stomach. The fundic wall was felt to be bulging into the esophageal lumen. The small resistance to flow from the esophagus into the stomach and the large resistance to retrograde flow suggested a flap valve mechanism at the cardia. This flap valve was thought to be formed by the sharp angle between the left wall of the lower esophagus and the right wall of the gastric fundus. His [28] described this angle as the "incisura cardiaca" and reproduced photographs of stomachs following varying degrees of filling, which seemed to indicate that this angle decreased with increased filling.

The experiments of Braune [5] and von Gubaroff [6] have been repeated under more controlled conditions. In summarizing these observations, a distinction should be made between the experiments on cadavers or excised specimens, and experiments on living animals or human subjects.

Kelling [29], after injecting air into the stomach of cadavers through a gastrostomy opening, found that the degree of filling necessary for the air to escape through the esophagus was quite variable. Marchand [30] found that the intragastric pressure necessary to induce reflux in young male cadavers was 28 cm. of water. The resistance to regurgitation at the cardia could be altered by changing the

anatomic conditions: Exclusion of the fundus from the remainder of the stomach reduced the required pressure to 9 cm. of water; removal of the organs surrounding the esophagus decreased the resistance to reflux to less than 3 cm. of water; removal of the left leaf of the diaphragm increased the resistance to 42 cm. of water. Marchand concluded that the oblique entry of the esophagus into the stomach acts as a flap valve when the stomach distends. Nauta [26], in determining the pressure required to induce reflux in resected gastroesophageal specimens, failed to demonstrate a valvular action at the cardia. Similar observations were reported by Adler and co-workers [37], who found that fluid flowed from the stomach into the esophagus just as readily as in the reverse direction, even when the esophagogastric angle was reconstructed. Increased resistance to regurgitation was observed only if the right wall of the distal esophagus was stabilized against a non-movable object.

Braune, von Gubaroff and Kelling did not measure the pressure that the cardia was able to withstand. The resistance at the cardia was estimated from the amount of air or fluid that could be injected into the stomach without resulting in gastroesophageal reflux. These pressures were measured in more recent studies, resulting in apparently contradictory data. A logical explanation for these apparently conflicting results is offered by Adler's work [37]. Removal of the organs surrounding the lower esophagus in cadavers may have the same effect as non-fixation of the right wall of the esophagus and stomach in excised specimens. An increase in intragastric pressure, under these circumstances, will act on the right gastric and esophageal wall as well as on the left side, resulting in failure to form a "flap valve." On the other hand, increased resistance after removal of the left leaf of the diaphragm may be explained by easier compression of the esophagus from the distended and bulging gastric fundus. This compression may be located at the height of the gastroesophageal angle, resulting in the formation of a flap valve, or it may be at a higher level of the esophagus. Exclusion of the gastric fundus has the same effect as creation of a tunnel. Under these circumstances, the force of an increase in intragastric pressure acts mainly and directly at the cardiac orifice [32]. Reflux is inevitable if this force is sufficiently strong.

The "cardia" offers little resistance to aboral

flow and great resistance to retrograde flow in cadavers, in which the normal anatomic relations are conserved, or in specimens with a fixed right gastroesophageal wall. This resistance can be changed by purely anatomic alterations. As these characteristics resemble the action of a flap valve, it has been concluded that the closing mechanism at the cardia is, in fact, a flap valve mechanism. Two objections may be raised to this conclusion: (1) although the facts strongly suggest a flap valve mechanism, this conclusion is based upon the similarity of action to a flap valve rather than on the actual demonstration of a flap valve; and (2) even if a flap valve exists in cadavers or excised specimens, it seems untenable to draw physiologic conclusions from experiments performed under these unphysiologic conditions.

Experiments have been carried out on living dogs and human subjects in an attempt to avoid this problem. Kelling [29] prepared a gastric fistula in dogs, and after four or five days he injected air into the stomach, measuring the pressures at which air escaped from the stomach into the esophagus. The unanesthetized animals usually actively regurgitated or vomited when the intragastric pressure reached 25 cm. of water. In the anesthetized animals, a pressure of 70 cm. of water against the gastroesophageal junction did not result in escape of air. Nauta [26] confirmed these observations and demonstrated that a pressure of 100 cm. of water was required to force water from the stomach into the esophagus of living, anesthetized dogs. A pressure of only 15 cm. of water was sufficient for flow to result in the opposite direction. Severing of the left side of the diaphragmatic loop around the esophagus reduced the required pressure from 100 to 30 cm. of water.

Schenk and Frederickson [33] found that the intragastric pressure necessary to produce opening of the cardiac sphincter and reflux into the esophagus was 40 cm. of water in lightly anesthetized cats. Straightening of the gastroesophageal angle did not result in a change in the pressure threshold. Adler and co-workers [37] observed that the cardiac angle itself was unable to prevent reflux if the right side of the esophagus was not stabilized against a non-movable wall. Esophagitis developed in dogs when the esophagogastric junction was removed, despite preservation of the acute esophagogastric angle and the diaphragmatic pinchcock [34,35]. When the acute esophagogastric angle was

eliminated without removal of the gastroesophageal junction, esophagitis did not result.

Marchand [30] studied the extent of regurgitation in ten young healthy male subjects while applying external pressure of 120 cm. of water to the abdominal wall. No reflux was noted in ten subjects who were given 500 ml. of thin barium. Regurgitation resulted in three subjects given 1,000 ml. of barium and in five subjects given 1,500 ml. of barium. Marchand concluded that distention of the stomach is an important factor in producing reflux of gastric contents. Neither intragastric pressure nor the gastroesophageal angle were measured. The technic used by Marchand is of limited value because pressure applied to the abdominal wall over the stomach is transmitted throughout the peritoneal cavity to the viscera adjoining the stomach [36].

If a flap valve is formed by the cardioesophageal angle, this angle should be acute when the gastric wall presses against the esophageal wall. However, the cardia may resist high intragastric pressure, even if the cardioesophageal angle is obtuse. In Dornhorst's experiments [3], reflux did not result even though the esophagus made a right angle with the gastric fundus. Further, the angle is completely obliterated in patients with near total gastrectomies, and yet the cardia often remains competent [32]. Although patients with pneumoperitoneum have a wide angle, no gastroesophageal reflux was noted [37,38].

On the other hand, in the condition described as "malpositions cardiotuberositaires" by Lortat-Jacob [39,40], the obtuse cardioesophageal angle is often accompanied by gastroesophageal reflux. However, other faulty mechanisms have not been excluded in this disease entity, in particular, the position of the high pressure zone in relation to the diaphragm has not been determined.

In summary, the experimental observations during life indicate that the cardia offers a greater resistance to retrograde than to aboral flow. The fact that a flap valve would act in a similar manner does not indicate that these characteristics are necessarily due to a flap valve mechanism. A definitive study correlating regurgitation with the gastroesophageal angle in human subjects has not yet been carried out.

THE DIAPHRAGMATIC PINCHCOCK

The esophageal hiatus of the diaphragm is formed by muscles derived from the right crus

of the diaphragm. Only in exceptional circumstances do fibers from the left crus participate in its formation. The right crus usually splits into a superficial (anterior) and a deep (posterior) lamella. The superficial lamella forms the right margin of the hiatus and the deep lamella crosses to form the left margin of the hiatus [41].

A constricting action of the hiatal muscle upon the esophagus during inspiration was described by Sauerbruch and von Hacker [42] in 1906. This has been called the diaphragmatic pinchcock [8] because it is said to close off the lumen of the esophagus as the result of lateral compression. The evidence in favor of the existence of a pinchcock mechanism has been based upon direct palpation of the lower part of the esophagus through a gastrostomy, during the course of experiments on animals, or during gastric operations on human subjects. Additional evidence has been supplied by observations during esophagoscopic and radiologic studies.

Sauerbruch and von Hacker [42] described rhythmic contractions synchronous with inspiration on direct palpation of the gastroesophageal junction in dogs. These contractions were not abolished by section of the vagi in the cervical region, but disappeared upon severing the diaphragmatic hiatus. They were able to locate the contractions exactly at the height of the diaphragmatic hiatus, by producing a small hiatal hernia, thus excluding a purely esophageal action. Joannides [43] described this type of contraction as a progressively downward milking action which could be made stronger when diaphragmatic breathing became more forcible and which reached its maximum following faradic stimulation of the diaphragmatic crura.

Feldman and Morrison [44] were unable to confirm a true milking action of the diaphragm upon the esophagus, but described the sensation produced by diaphragmatic contractions as a tug against the palpating finger which was lessened when the hand moved in the direction of the movement of the diaphragm.

Preservation of the diaphragmatic pinchcock, following resection of the gastroesophageal junction, did not prevent reflux in dogs [34], but splitting of the diaphragm and resection of the cardia from its ligamentous attachments resulted in a decrease in the amount of intragastric pressure necessary to produce opening of the cardiac sphincter [33].

The observations on human subjects in respect to the action of the diaphragmatic

pinchcock are even more controversial than those on experimental animals. Some authors state that the muscular contractions of the pillars of the crura during inspiration can be felt by the palpating finger [45-47]. Others deny this [3,30].

From the observations on dogs, it is evident that there must be some kind of constriction of the lower part of the esophagus during inspiration. The differences of opinion as to the exact nature of this constriction in dogs and the dispute concerning the presence or absence of such a mechanism in human subjects is probably due to one or more of the following factors: (1) the depth of anesthesia, the degree of muscular relaxation and the depth of respiration; (2) the type of respiration, costal, thoracic or abdominal; (3) the size of the hiatus; and (4) the difference of the subjective impression of the various observers.

The esophagoscopic evidence for a diaphragmatic pinchcock was considered by Jackson [8] to be so obvious that no dispute seemed possible. The esophageal lumen could be observed to open with inspiration and to close with expiration. This was especially noticeable at the level of the diaphragmatic hiatus. It is impossible, however, for the esophagoscopist to determine whether the observed narrowing is due to a "ring-like" contraction produced by the diaphragm or to a "tube-like" compression resulting from the increased intrabdominal pressure secondary to inspiration.

The fact that a barium swallow may be held up at the level of the diaphragm on deep inspiration has been interpreted as an argument in favor of the constricting action of the diaphragm upon the esophagus. That the delay may occur well above the apparent diaphragmatic shadow does not invalidate this argument. By attaching metal clips to the hiatal walls, it has been shown that in some positions the diaphragmatic hiatus projects markedly above the diaphragmatic shadow [48]. On the other hand, the anterior portion of the diaphragm is higher and in many instances overlaps the zone of high pressure.

A delay in the passage of barium on radiologic study does not necessarily indicate that this delay is a result of the pinchcock action of the diaphragm. Intra-abdominal pressure increases and reaches a level well above intrathoracic and intraesophageal pressures on inspiration. This pressure differential is more than sufficient to explain the delay of passage of barium from

the esophagus to the stomach. Inspiration does not result in a ring-like obliteration of the esophageal lumen at the height of the diaphragm [49]. Actually, the whole infra-diaphragmatic esophagus is empty suggesting that this entire segment is either compressed or contracted.

The influence of diaphragmatic contractions upon the lower part of the esophagus has been studied by means of a sausage-shaped balloon which was filled with radiopaque fluid and introduced into the lower portion of the esophagus [48]. Normal respirations did not have a constricting effect upon the balloon. Deep, forced respirations resulted in a complete ring-like obstruction of the lumen, suggesting compression by the diaphragmatic pillars. Failure of the intra-abdominal portion of the balloon to collapse merely indicates that the force produced by the diaphragmatic pinchcock is more powerful than that produced by increased intra-abdominal pressure under these circumstances.

Phrenectomy has been used to study the role of the diaphragm in the gastroesophageal closing mechanism. The results of right phrenectomy are of limited significance for it is known that both the right and left phrenic nerves participate in the innervation of the bundles of muscle encircling the diaphragmatic hiatus [50]. Following complete paralysis of the diaphragm secondary to bilateral phrenectomy in dogs, no reflux of gastric contents resulted when the dogs were in the head down position or following increased intragastric pressure [44].

In summary, the evidence indicates that contraction of the diaphragm during normal respiration does not seem to play an essential role in the prevention of reflux. The diaphragm may exert an indirect influence upon the "high pressure zone" [8,11,12,51,52].

THE CARDIAC ROSETTE

Closure of the cardiac orifice by folds of gastric mucosa which have the appearance of a rosette, was suggested by Magendie in 1833 [7]. Kelling [29] also observed occluding folds in the cardia during his regurgitation experiments on anesthetized dogs. This concept was not accepted since the occluding folds could be demonstrated only rarely in postmortem specimens of animals or man.

Until recently, most of the evidence in favor of the cardiac rosette was of an indirect nature. Dornhorst [3] studied the closing mechanism of the esophagus by intraluminal pressure measure-

ments, roentgenograms, direct palpation of the cardia and lower portion of the esophagus during gastrotomy, during the course of gastric operations, and by observation of the gastroesophageal angle during regurgitation. He reported no evidence for either a physiologic sphincter, a pinchcock action of the diaphragm or a flap valve formed by the gastroesophageal angle. As the small resistance to forward pressure and the ability to resist retrograde flow in spite of much larger pressures suggested a valve mechanism, Dornhorst concluded that some sort of mucosal valve must exist. Creamer [53], on the basis of his observations on gastroesophageal reflux produced by carminatives, favored a similar mechanism. Carminatives result in hyperemia of the gastric mucosa which interferes with closure of the mucosal folds and thereby results in reflux.

Direct observations in the cardia during life have been variously interpreted. Sinnhuber [27] described the resting cardia of rabbits and dogs as a projecting papilla. However, Schreiber [54] reported that the innermost surface of the cardia in rabbits did not differ from the adjoining gastric mucosa. Feldman [44] found that the gastric rugae converged toward the gastroesophageal orifice in dogs, an observation that was confirmed by Nauta [26].

The most extensive observations were those of Botha [32] who studied cadavers, several species of animals, and human subjects during life. By careful palpation of the cardiac orifice during the course of gastric observations, he found evidence of occluding folds in every patient. These folds were rarely seen in cadavers, presumably because of postmortem changes. Various types of folds were seen in animals, many of which resembled a rosette which constantly changed in shape, form and position. Although the changes appeared to be mainly dependent upon alterations in tone of the surrounding musculature, an active and independent tone was thought to be present in the folds, presumably as the result of activity of the muscularis mucosae.

The evidence in favor of a "mucosal valve" mechanism is not very conclusive. Dornhorst's conclusions favoring a cardiac rosette were based upon the premise of the absence of a physiologic sphincter. Creamer did not study the effect of carminatives on the pressures of the lower esophageal segment and a relaxant effect upon the sphincteric segment was not excluded.

Botha's observations leave little doubt that a cardiac rosette is present in many animals and man, at least during life. However, regurgitant esophagitis did not develop in any of the animals studied by Meiss, Grindlay and Ellis [34] in whom the mucosal rosette was eliminated.

Anesthesia, transection or manipulation of the wall of the cardia may result in functional alterations in the cardiac region [27,32]. Botha maintained that the gastric folds about the cardia have muscular activity independent of the surrounding musculature which he attributed to the muscularis mucosa. The possibility that this activity is related to changes in tone of the lower esophageal segment has not been excluded. Tight contraction of any sphincter usually results in converging folds of the overlying mucous membrane [55].

In summary, the evidence in favor of the mucosal valve is not sufficiently conclusive to indicate that it plays a primary role in the closing mechanism of the gastroesophageal junction.

THE PHYSIOLOGIC SPHINCTER

Although an anatomic sphincter has not been conclusively demonstrated at the cardioesophageal junction, the physiologic characteristics of this zone are those of a sphincteric mechanism. The term physiologic sphincter seems warranted.

The older data suggestive of a sphincteric action include the demonstration that the cardia is normally closed, but that this closure can be made incompetent by reflex means as evidenced by regurgitation, and that various gastric stimuli increase the resistance to gastroesophageal reflux [56]. The resting lower esophageal segment is normally closed at esophagoscopy [27,57,58]. Direct observation of the cardia from the gastric side has led to the same conclusion [32,44]. Lesions caused by ingestion of lye do not occur in the lowermost 2 or 3 cm. of the esophagus. This has been interpreted as being indicative of a state of normal "closure" of this segment. However, the irritating effect of lye may induce spastic contractions of the lower portion of the esophagus, tending to invalidate this argument. Radiologic examination of the resting esophagus also reveals that the lowermost segment is empty.

All these observations indicate that the lower esophageal segment normally is closed but they give no indication as to the mechanism of this closure. Closure could result from either tonic

contractions of the esophageal musculature or as a result of other factors.

Arguments in favor of the reflex opening of this closed segment are found in several older investigations. Regurgitation from an air- or fluid-filled stomach in animals occurs when the lower esophageal wall is stimulated mechanically by a gastric tube, without the tube reaching the sphincteric zone [42,44,56]. Swallowing or distention of the esophagus has a similar effect [27,57,58]. Vagal stimulation lowers the threshold of intragastric pressure necessary to produce opening of the cardiac sphincter [33]. Regurgitation from the barium-filled stomach may occur if the abdominal pressure is sufficiently increased [30]. These data indicate that swallowing, distention or stimulation of the esophagus facilitates regurgitation but they do not clearly delineate the mechanism responsible for this regurgitation.

The resistance at the cardia to either aboral flow into the stomach or to gastroesophageal reflux can be increased by reflex means. The pressure required to force fluids from the esophagus into the stomach was increased when the region of the cardia was stimulated chemically or mechanically in human subjects [56]. Distention of the gastric wall, irritation of the gallbladder and distention of the intestines result in an increase in cardiac tone as measured by the balloon-kymograph system [59]. Cannon [60] showed that rhythmic gastroesophageal regurgitation occurred after the infusion of 180 ml. of a radiopaque fluid into the stomach of cats. This regurgitation could be strongly inhibited by increasing the acidity of the gastric contents. Carlson and Luckhardt [61] demonstrated that gastric air is not forced into the esophagus during forceful gastric hunger contractions and that the resistance to the withdrawal of a distended balloon about the size of a finger was distinctly increased at the height of such hunger contractions.

The observations of Jourdan and Faucon [62,63] favor the concept of a physiologic sphincter at the lower end of the esophagus. They studied the transport of barium in the esophagus of dogs after bilateral vagotomy with and without excision of both stellate ganglia and concluded that the lower 4 cm. of the esophagus acts as a separate unit capable of opening and closing by reflex means. Fyke, Code and Schlegel [9] demonstrated a zone in the lower end of the esophagus where the resting

pressures are higher than in the gastric fundus regardless of the position of the subjects. (Fig. 1.) This zone has been termed the "high pressure zone." The pressures in this segment, which extend from 1 to 2 cm. below the diaphragm to 1 to 2 cm. above the diaphragm, are such that during both phases of respiration there is an area of high pressure between the stomach and the esophagus. The pressures in this zone fall 1.5 to 2.5 seconds after the onset of deglutition, thus abolishing this barrier. This decrease in pressure lasts from five to six seconds, until a peristaltic wave reaches this segment. These observations have been confirmed by a number of investigators [10-12,64,65]. Further confirmation has resulted from studies using simultaneous intraluminal pressure measurements with fluorocinematography [51,66]. Distention of the esophagus, secondary contractions [65,67], or taking liquids into the mouth [68] may result in a decrease in pressure in this zone. A sphincteric zone operating similarly at the esophagogastric junction has been demonstrated in dogs [33,62,63,69].

The resting pressures in this zone have been interpreted as being the result of tonic contraction of the circularly arranged muscle fibers in this segment [9]. Subsequent studies of Kelley, Schlegel and Code [70] indicate that the upper portion of this zone is characterized primarily by relaxation whereas the lower portion of this zone is characterized primarily by contraction.

The high resting pressures of this zone might also be attributed to external compression. The fall in pressure following deglutition or other stimuli might result from a reflex abolition of this compression. The diaphragm is the only organ capable of participating in such a mechanism. Physiologic studies on patients with sliding hiatal hernia have indicated that the high pressure zone, when present, is found at the junction between the esophagus and the herniated stomach [52,71]. At this site, a localized narrowing is often seen radiologically [52,72,73], and there is a weak barrier to regurgitation from the herniated stomach into the esophagus [52,71]. These observations strongly corroborate the concept that an intrinsic esophageal sphincter mechanism is responsible for the high pressure zone.

Further evidence in support of the view that an intrinsic sphincter mechanism is normally present is afforded by the observations on patients with scleroderma who, despite the normal

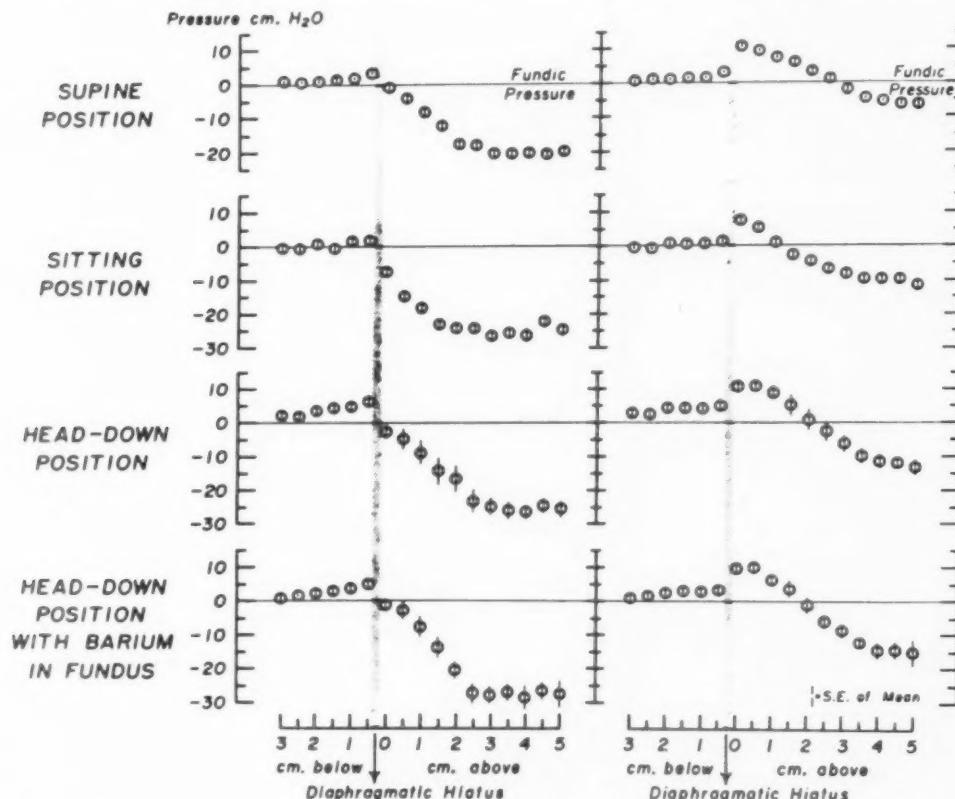


FIG. 1. Mean resting pressures at the gastroesophageal junction plotted in relation to fundic pressure in centimeters of water. Study of nineteen healthy persons. (From: CODE, C. F., CREAMER, B., SCHLEGEL, J., ALSEN, A., DONOGHUE, F. E. and ANDERSON, H. A. An Atlas of Esophageal Motility in Health and Disease, p. 47. Springfield, Ill., 1958. Charles C Thomas.)

anatomic relationship between the gastroesophageal vestibule and the diaphragm, have a decrease in, or absence of, the high pressure zone at the gastroesophageal junction. This physiologic alteration is a result of sclerodermatous changes of the esophagus [12,74,75]. Gastroesophageal reflux is exceedingly common in this group of patients.

Fyke, Code and Schlegel [9] demonstrated that the high pressure zone is below the diaphragm at the height of inspiration and partly below but mostly above the diaphragm at the end of expiration. (Fig. 2.) When the diaphragm descends on inspiration, the high pressure zone also descends, and when the diaphragm moves upward, on expiration the high pressure zone is found mainly above the diaphragm. In order to explain the curious behavior of the high pressure zone, the definition of this zone as given by Fyke et al. [9] might be recalled; namely, that this is the segment of the lower portion of the esophagus where the resting pressures are higher than pressures in the gastric fundus.

The pressures in the lower part of the esophagus result not only from the state of contraction of the esophageal wall, but also are greatly influenced by extraesophageal respiratory pressure variations in the thoracic and abdominal cavities. If it is accepted that the physiologic sphincter is normally in a state of tonic contraction; and, if it is further accepted that this contraction is such that the extraesophageal respiratory variations can have an influence on intraesophageal pressures in this segment, then the changes in the pressures in this segment become more understandable. On inspiration, intrathoracic pressure decreases and results in a decrease in the lateral pressure surrounding the superdiaphragmatic portion of the physiologic sphincteric segment. The pressures of the infra-diaphragmatic portion of the sphincteric segment not only escape the influence of the increased negative pressure of the thorax during inspiration, but also are reinforced by the greater positive intra-abdominal pressure during this phase of respiration. (Fig. 3.) This appears

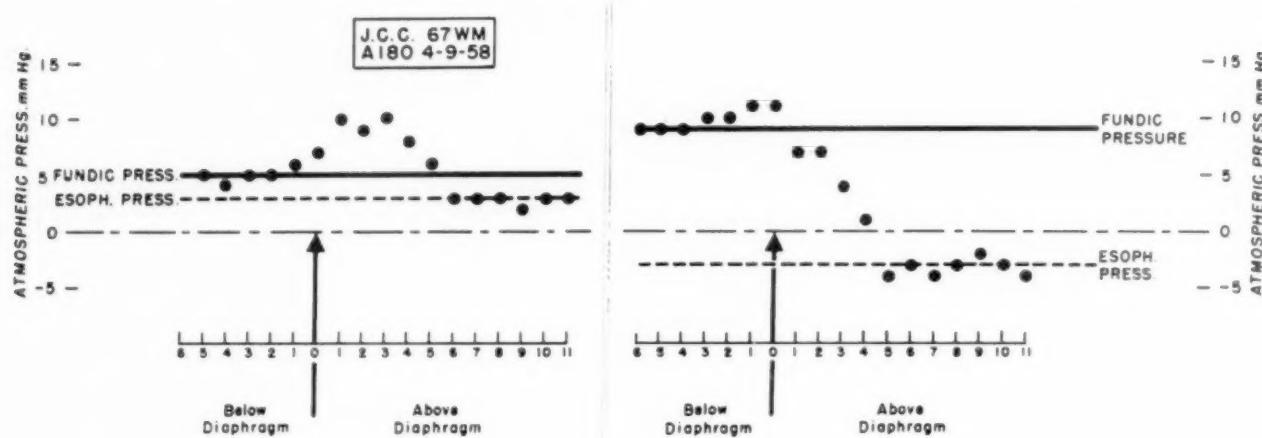


FIG. 2. End-expiratory pressures (left) and end-inspiratory pressures (right) in the gastroesophageal region in relation to fundic, esophageal, and atmospheric pressure in millimeters of mercury. (From: VANTRAPPEN, G., LIEMER, M. D., IKEYA, J., TEXTER, E. C., JR. and BARBORKA, C. J. *Gastroenterology*, 35: 592, 1958 [57].)

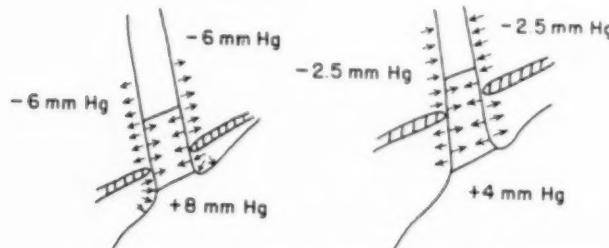


FIG. 3. Schematic diagram indicating the effect of extra-esophageal pressures on the behavior of the high pressure zone in relation to respiration. *Left*, inspiration. *Right*, expiration.

to account for the fact that the high pressure zone is below the diaphragm at the end of inspiration. On expiration, the reverse situation exists. Intrathoracic pressures become less negative, resulting in an increase in pressure in the supradiaphragmatic portion of the sphincteric segment. It is evident, therefore, that the whole physiologic sphincter is not located beneath the diaphragm at the end of inspiration but is still partly below and partly above the diaphragm. However, only the pressures in the infradiaphragmatic portion are higher than those recorded from the gastric fundus. At the end of expiration only the infradiaphragmatic portion of the physiologic sphincter corresponds to the high pressure zone. At the end of inspiration the physiologic sphincter also consists of both a supra- and infradiaphragmatic component. However, the highest pressures are recorded from the supradiaphragmatic portion.

Respiratory pressures accompanying inspiration result in a positive deflection when

the intraesophageal catheter is located below the diaphragm, and a negative deflection when the catheter is located above the diaphragm. The point where reversal takes place has been assumed to correspond to the level of the diaphragmatic hiatus. When a pressure sensitive device is placed just below this level, a biphasic deflection is often observed on deep inspiration. The initial positive respiratory wave reverses and becomes negative during continued inspiration. On deep inspiration the catheter tip appears to pass from the peritoneal cavity into the thoracic cavity [37]. The most likely explanation for this phenomenon assumes that the diaphragm pinches off the esophageal lumen, even during normal respiration. However, if it is assumed that the entire infradiaphragmatic portion of the esophagus is normally collapsed, not only as the result of diaphragmatic contraction, but also as the result of high lateral intra-abdominal pressure, pinching off of the esophageal lumen would not be necessary to explain the observed facts. On inspiration, the diaphragm descends, and the uppermost part of the initially infradiaphragmatic collapsed segment becomes supradiaphragmatic and escapes the higher intra-abdominal pressure. Although this appears to be a tenable working hypothesis, further experimental and radiologic confirmation will be required.

The fact that the pressure in the physiologic sphincter gradually increases upon approaching the diaphragmatic hiatus and reaches a maximum at this level has not yet been adequately explained. Diaphragmatic compression can be

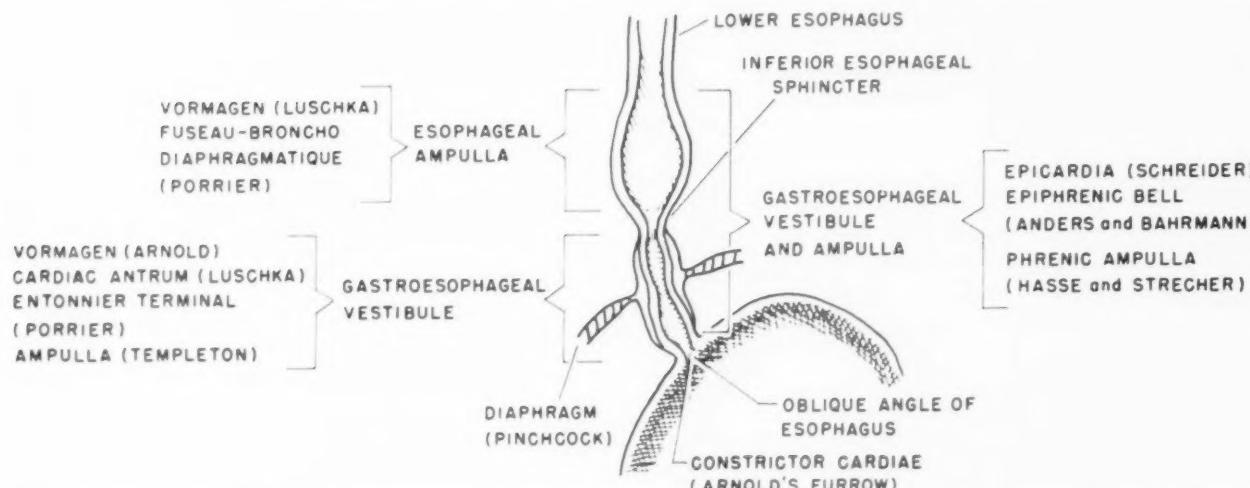


FIG. 4. Schematic diagram of the anatomy of the gastroesophageal junction according to Lerche [24] and others.

excluded as a possible cause, for even at the end of expiration when the diaphragmatic hiatus should be open, the point of maximum pressure is still at this level.

Lerche's [24] observations have provided an anatomic setting which has been correlated with the physiologic observations. Lerche's studies led to the description of the gastroesophageal vestibule, a dilatation extending from the cardia to 1 cm. above the diaphragm. Lerche described two sphincters, one at the proximal end of the vestibule which he termed "the lower esophageal sphincter," and one at the distal end, which he termed "the constrictor cardiae." As already noted, it is evident that what he terms a sphincter does not represent a true anatomic sphincter in the sense that it is a distinct muscular segment enclosed in a fascial sheet. In addition, Lerche described another dilatation above the level of the vestibule which he termed the "ampulla." (Fig. 4.)

Although the Lerche nomenclature has been used by many investigators [2,10-12,37,51,65,66, 76], the terminology of the distal esophagus and esophagogastric junction remains confused. This confusion has existed since 1838 when Arnold [77] described two furrows in the lower part of the esophagus which contained between them an expanded structure of the esophagus. The lower furrow was probably the structure we today consider the cardia and was previously known as "Arnold's furrow." The second furrow was situated about 3 cm. orally but the level of this furrow in relation to the diaphragm was not stated. Arnold considered the expanded portion of the esophagus to be the human counterpart of the anterior stomach of the ruminant-

ing animal and termed this structure the "vormagen."

Luschka [78], in 1857, described the lower portion of the esophagus as having two forms. One form was identical with that described by Arnold except that Luschka placed the upper furrow of Arnold at the level of the diaphragm and termed the expansion between the two furrows as the "cardiac antrum." The second form included all the characteristics of the first with the addition of a second expansion of the esophagus above the level of the diaphragm. He termed this expansion the "vormagen." Thus Luschka calls Arnold's "vormagen" the "cardiac antrum" and applies the term "vormagen" to the second dilatation above the diaphragm. In 1901, Schreiber [79] introduced the term "epicardia" for the lowermost 4 to 5 cm. of the esophagus above the diaphragm. This area was subsequently termed the "epiphrenic bell" [80]. Templeton [81] notes that Hasse and Strecker [82], in 1905, were probably the first to publish the term "phrenic ampulla" as a designation for the dilatation of the esophagus above the diaphragm. This term came into common usage by radiologists. Poirier et al. [83] used the term "entonnier terminal" for the "cardiac antrum" and the term "fusseau-broncho-diaphragmatique" for the dilatation above the diaphragm. An attempt has been made to correlate these terms with the Lerche terminology in Figure 4.

According to Templeton [84,85] the vestibule of Lerche corresponds to what has been termed the ampulla by radiologists. The ampulla of Lerche is the site where the esophageal peristalsis slows down as observed radiologically and by manometric measurements [2,9].

The conclusions of Lerche as to the functional phenomena were based upon anatomic dissections. Correlations with roentgenographic and other *in vivo* findings were unimpressive. The question remains unanswered as to whether the vestibule, inferior esophageal sphincter or cardiac sphincter could be demonstrated *in vivo*. Wolf and co-workers [76] described two narrowings of the esophagus at its junction with the stomach in their radiocinematographic studies, a proximal one termed "A," a distal one termed "B." The distal narrowing was observed only in the presence of a direct hiatal hernia since normally the distal narrowing is located in or below the diaphragm and is therefore limited in distensibility by extrinsic factors. They concluded that the vestibule of Lerche corresponded to the high pressure zone. Although this assumption seems reasonable, it still awaits confirmation by combined radiocinematographic and pressure studies.

The problem of the identity of Lerche's vestibule and the radiologic ampulla remains unsettled. The vestibule extends from the level of the cardia to 1 to 2 cm. above the diaphragm. The radiologic ampulla extends from the level of the diaphragm (or of the lower esophageal sphincter) to several centimeters higher up. If these terms mean the same thing it must be assumed that at the moment of formation of the ampulla no abdominal esophagus exists. Although this is not impossible, it has not been proved.

On the other hand the constriction at the apex of the radiologic ampulla appears to move downwards [87] resulting in a diminution of the size of the ampulla. When this is due to a constricting ring that progresses distally and not to a contraction of the ampulla as a unit, then the radiologic ampulla cannot correspond to an anatomic entity, or to a high pressure zone with more or less constant dimensions. Further studies will be required to clarify this point.

The high pressure zone probably corresponds to the vestibule of Lerche. The ampulla of Lerche may correspond to the site of slowed peristalsis. It is possible that the radiologic ampulla corresponds to the vestibule of Lerche, but this is rather unlikely.

In summary, the studies seem to indicate that, from the standpoint of functional anatomy, the lower few centimeters of the esophagus have definite characteristics, permitting one to recognize this area as a functional unit, different

from the remainder of the esophagus. This area has been characterized physiologically as a sphincter, but the physiologic findings have not been satisfactorily correlated with the anatomic observations or with the radiologic data. The physiologic sphincter appears to play the major role in preventing gastroesophageal reflux.

SUMMARY AND CONCLUSIONS

Several mechanisms have been suggested to explain the absence of gastroesophageal reflux despite a negative pleuroperitoneal pressure gradient. These include: an anatomic sphincter, a flap-like mechanism, a pinchcock action of the diaphragm, an occluding rosette of mucosal folds and a physiologic sphincter. The experimental and clinical data relating to each of these factors have been reviewed and discussed. The following conclusions may be drawn:

1. A distinct anatomic sphincter does not exist at the cardioesophageal junction. A U-shaped band of muscle fibers derived from the oblique fibers of the stomach is a constant finding at the cardiac incisura. Contraction of these muscle bundles may result in closure of the cardiac orifice.

2. A flap valve has never been convincingly demonstrated. The experiments on cadavers or excised specimens are of little value because no conclusions as to function during life can be drawn. Although a difference in resistance to aboral and retrograde flow is found in living animals and man, it has not been established that this is a result of a flap valve mechanism. In addition to the lack of convincing evidence for a flap valve mechanism, other factors render the study of this problem difficult. Resistance of the lower esophageal sphincter to aboral flow cannot be measured because reflex relaxation of the sphincter precludes this measurement. The tonus of the physiologic sphincter may increase following gastric stimuli, presumably as the result of reflex contraction.

3. A pinchcock action of the diaphragm probably does not exist except during deep inspiration. The delay of barium transport above the diaphragm, which is observed roentgenologically, is probably caused by the difference in gastroesophageal pressure. Although esophageal constriction by the diaphragmatic hiatus may play a role in the prevention of regurgitation during deep inspiration, the diaphragmatic constriction is not essential for an

efficient closing mechanism. Reflux does not occur during expiration while in the head-down position and reflux occurs only during inspiration when the constricting action of the diaphragm should be minimal. Bilateral phrenectomy does not result in reflux either in the head-down position or following application of increased intragastric pressure.

4. During life, a rosette of mucosal folds can be demonstrated about the cardiac orifice in man and in many species of animals. This arrangement of the gastric rugae changes in shape, form and position. It is not clear whether this change is a result of an alteration in tone of the lower esophageal segment or due to the action of the muscularis mucosae. The role of the rosette in the closing mechanism of the esophagus cannot be much more than to secure a water tight seal of the cardiac orifice which has already been closed by another mechanism.

5. Intraluminal pressure studies clearly demonstrate that the lower few centimeters of the esophagus act as a physiologic sphincter. The high resting pressures in this segment appear to be the result of tonic contractions of the circularly arranged muscle fibers. Several stimuli result in a fall in pressure in this zone probably as the result of reflex relaxation of these muscles. The pressures in this sphincteric segment are such that during each phase of respiration the whole zone or part of it acts as a barrier against gastroesophageal reflux. This barrier against reflux has been termed "the high pressure zone" because the pressures are higher than those in the gastric fundus. At the end of inspiration only the infradiaphragmatic portion of the physiologic sphincter acts as a barrier against reflux. At the end of expiration the whole physiologic sphincter fulfills this function. The infradiaphragmatic portion of the physiologic sphincter is the more important one since it is the only portion that prevents reflux at the moment when regurgitation is strongly favored by the high peritoneal-pleural pressure gradient. The normal anatomic relationship between the diaphragm and esophagus resulting in a portion of the physiologic sphincter being located below the diaphragm, appears to be important for proper functioning of the closing mechanism.

6. Although the high pressure zone appears to play the primary role in the closing mechanism at the gastroesophageal junction, it is unlikely that it is the only factor involved.

7. The terminology relating to the lower few

centimeters of the esophagus remains confused. It is probable that the high pressure zone and the gastroesophageal vestibule are identical. This zone with its adjoining sphincters appears to act as a unit. The relationship between the vestibule and the radiologic ampulla remains controversial.

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Gallop Rhythm of the Heart*

I. Atrial Gallop, Ventricular Gallop and Systolic Sounds

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DURING the one hundred years since the first description of cardiac gallop rhythm a variety of extra heart sounds, both systolic and diastolic, have been placed in this category. "Triple rhythm" and "gallop rhythm" are often used synonymously and interchangeably to denote the presence of a sound in addition to the normally occurring first and second heart sounds. Most observers do not include in this category the extra sounds caused by asynchronous closure of valves, i.e., splitting of the first or second heart sound. Even with this restriction gallop rhythm includes many sounds, each with a different etiology and representing as many different cardiac events. Lacking specificity as a descriptive term, gallop rhythm has little clinical implication or significance and no unique hemodynamic meaning.

The advent of simultaneous phonocardiography, electrocardiography and mechanocardiography (i.e., pressure recordings, kymography and ballistocardiography) has provided greater understanding of cardiac events and their associated sounds. Although admittedly incomplete, our present knowledge dictates a re-definition of nomenclature so that descriptive terms will be conceptually unique and thereby possess the specificity desired by physiologist and clinician alike.

A useful definition is as follows: Cardiac gallop is a mechanical hemodynamic event associated with a relatively rapid rate of ventricular filling and accompanied by a ventricular bulge and a low-frequency sound.

From this definition several features of the cardiac gallop are evident. First, ventricular filling occurs during diastole and hence a gallop is diastolic in time. Systolic sounds of any

origin are thereby excluded from the category of gallop and must be appropriately named.

Second, of the five divisions of diastole—protodiastole of Wiggers, isometric ventricular relaxation, rapid ventricular filling, slow ventricular filling and atrial contraction—a relatively rapid rate of ventricular filling occurs only during two of these periods, namely, (1) the rapid filling phase, which follows immediately upon opening of the A-V valve, and (2) the atrial phase, which follows contraction of the upper chamber. We can conveniently and descriptively name the gallops associated with these two periods as rapid filling (or ventricular) gallop and atrial gallop. The designation of the rapid filling gallop as "protodiastolic" is an unfortunate misnomer as the gallop does not occur during the physiologic protodiastolic period. Both the rapid filling gallop and the atrial gallop may be generated in either ventricle. Therefore, it is desirable to specify whether the gallop originates from the right or left side of the heart.

Third, a gallop may occur at any heart rate and is in no way restricted to periods of tachycardia.

Fourth, the associated mechanical aspects of the gallop may be recorded and are useful in the recognition and understanding of the gallop. The electrokymogram has demonstrated abnormal expansive movements of the left ventricular border which are related to the gallop sound [1,2]. These diastolic inflections are detected more regularly by slit roentgenkymography than by electrokymography [2].

Large ballistic forces directed toward the right shoulder occur at the time of gallop [3,4] and may be of differential diagnostic value

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TABLE I

Case No.	Patient	Heart Rate (beats/min.)	Time Intervals* (sec.)				Fundamental Frequency of Gallop Sound (c.p.s.)
			P - AG	AG - 1	P-R	Q - 1	
1	W. H.	65	0.17	0.06	0.20	0.03	30
2	C. H.	67	0.15	0.11	0.18	0.08	40
3	R. S.	73	0.14	0.11	0.16	0.09	40
4	W. B.	77	0.14	0.16	0.20	0.10	50
5	R. V. J.	77	0.14	0.10	0.17	0.07	50
6	W. T.	83	0.12	0.10	0.16	0.06	40
13	E. C.	84	0.12	0.15	0.20	(0.07)	25
14	W. O. H.	96	0.12	0.10	0.15	(0.07)	50
			0.138 (average)			0.072 (average, only cases 1-6)	

* P - AG = interval from onset of P wave to onset of atrial gallop.

AG - 1 = interval from onset of atrial gallop to the first heart sound.

P-R = conventional electrocardiographic interval.

Q - 1 = interval from onset of QRS complex to the first heart sound.

between the gallop and other sounds. In the same patient the ballistocardiogram has often recorded a gallop wave larger than the waves of ventricular systole. When the chest wall is not excessively thick the localized gallop thrust can be appreciated at the chest surface by inspection or palpation. Variations in the physical properties of chest walls naturally affect the ease with which these thrusting forces can be sensed at the surface. When a gallop bulge appears on the surface of the chest the apex cardiogram affords an easy method for recording this movement.

Gallops bear a definite relation to portions of the jugular phlebogram. The rapid filling or ventricular gallop coincides with the Y descent of the V wave. The atrial gallop follows the A wave by a short interval (0.07 second) [5]. Thus a sound is only one manifestation of a mechanical event we call the gallop.

METHOD

Simultaneous phonocardiogram-electrocardiogram and phonocardiogram-apex cardiogram were recorded on a Sanborn Twin-beam model 62 at a paper speed of 75 mm./second with time lines every 0.04 second. Patients were in the supine position, occasionally turned slightly toward the left side to accentuate precordial pulsations.

Local precordial movements were recorded from the chest wall in the region of maximum cardiac pulsation (inaccurately termed apex cardiogram)

by placing a spherical cup against the chest wall to form an air-tight seal between the circular cup edge and the skin. Changes in air pressure effected within the cup by local movements within were transduced by a piezoelectric device. An upward deflection on the tracing represented outward movement of the thoracic surface.

Phonocardiograms were recorded simultaneously with each of the three standard bipolar extremity leads. The onset of a gallop sound was taken as the start of its first vibration. The onset of the first heart sound was taken as the onset of the first high-frequency component of this sound. In patients with atrial gallop the interval between onset of the P wave and the atrial gallop sound was measured employing the standard bipolar limb lead which demonstrated the earliest onset of the P wave. This was determined by the longest interval among the three limb leads from the onset of the P wave to the atrial gallop, and therefore, also to the first heart sound on the simultaneous phonocardiogram. In most instances limb lead II was employed.

ATRIAL GALLOP RHYTHM

Observations

Atrial gallop sounds were recorded in eight patients. In six of these the atrial gallop was the only additional heart sound. In two patients both atrial and rapid filling gallops were present; these two are described elsewhere [6]. Time intervals within each cardiac cycle associated with the atrial gallop in these eight cases appear in Table I.

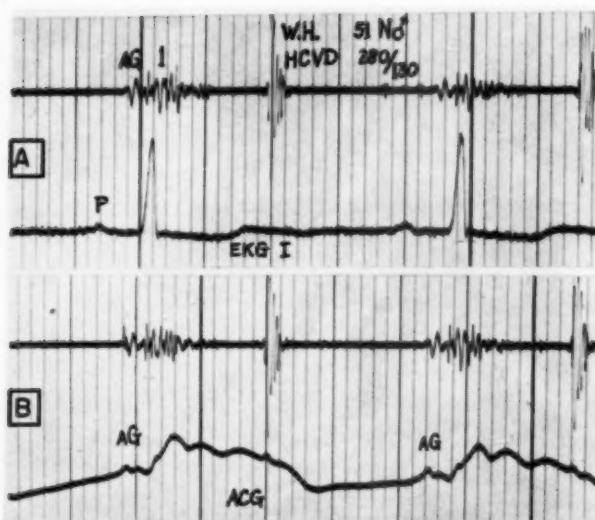


FIG. 1. Case 1. A, simultaneous phonocardiogram and electrocardiogram, lead I. B, simultaneous phonocardiogram and apex cardiogram (ACG). The low-frequency atrial gallop (AG) precedes the electrical QRS complex and is simultaneous with a gallop movement of the apical region, recorded as a small summit (AG) on the apex cardiogram. The minute heart rate is 65.

CASE 1. W. H. was a fifty-one year old Negro man with essential hypertension. The blood pressure was 280/130 mm. Hg. There was questionable left ventricular hypertrophy but no evidence of heart failure. A localized presystolic impulse could be seen and felt at the point of maximum cardiac pulsation and a corresponding low-pitched sound was audible. An electrocardiogram gave evidence of left ventricular hypertrophy with tall QRS complexes and S-T segment and T wave abnormalities.

The phonocardiogram (Fig. 1A) showed the loud presystolic sound with a fundamental frequency of 30 c.p.s. The gallop preceded the QRS of the electrocardiogram and occurred simultaneously with a small summit on the apex cardiogram. (Fig. 1B.)

Comment: The only evidence of myocardial disease was the presence of an atrial gallop rhythm and electrocardiographic abnormalities indicative of left ventricular hypertrophy. Heart failure was absent.

CASE 2. C. H. was a sixty-five year old Negro man with well documented hypertension for many years. At the time of study the blood pressure was 130/94 mm. Hg. Grade 2 hypertensive retinopathy was present. There was slight left ventricular hypertrophy, confirmed by teleroentgenogram which also demonstrated a tortuous, elongated aorta. A prominent presystolic impulse was present at the area of maximal apical pulsation. The simultaneous low-pitched gallop sound was soft. The electrocardiogram revealed left deviation of the axis of QRS with inverted T waves in leads II and III.

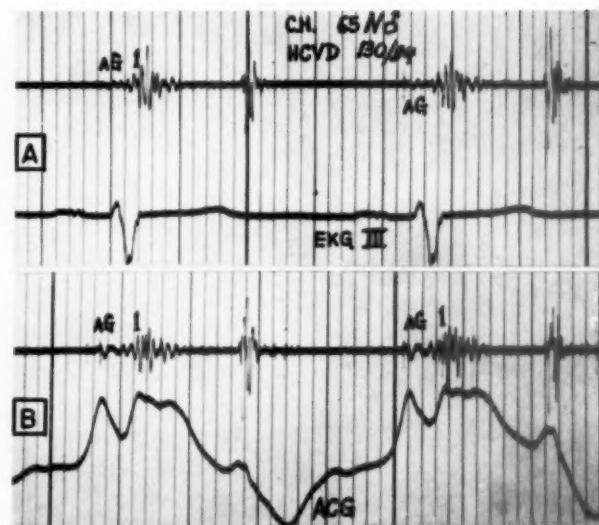


FIG. 2. Case 2. A, simultaneous phonocardiogram and electrocardiogram, lead III. B, simultaneous phonocardiogram and apex cardiogram (ACG). The atrial gallop (AG) begins prior to the onset of the QRS complex and is simultaneous with a prominent upward deflection on the apex cardiogram, which represents a large forward apical movement. The minute heart rate is 67.

A phonocardiogram (Fig. 2A) demonstrated the onset of the gallop sound just prior to the first deflection of QRS in the simultaneous electrocardiogram. The apex cardiogram (Fig. 2B) illustrated the prominence of the presystolic ventricular bulge.

Comment: This patient had long-standing systemic hypertension with resultant myocardial hypertrophy. Despite a normal blood pressure at the time of the recording the atrial gallop persisted. It would appear, therefore, that secondary myocardial changes rather than an elevated blood pressure *per se* are essential to the production of the gallop.

In this patient the mechanical feature of the gallop, i.e., the ventricular bulge, was more prominent than the acoustic feature. There was no evidence of heart failure. The left ventricle was hypertrophied.

CASE 3. R. S., a fifty-seven year old white man, was seen because of a mild acute episode of bronchial asthma known to be evident for more than twenty years. Hypertension was well documented during the last seven of these. After subsidence of the acute attack physical examination revealed a blood pressure of 170/90 mm. Hg. There was mild emphysema manifested by increased anteroposterior diameter of the chest and hyperresonance. The heart was not enlarged and the cardiothoracic ratio on roentgenographic examination was 15:31. A cardiac impulse was not visible and barely palpable due to the emphysema. A low-pitched presystolic gallop sound was

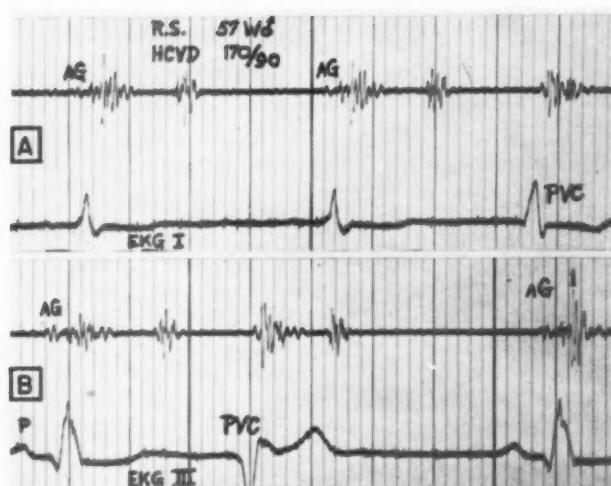


FIG. 3. Case 3. Simultaneous phonocardiogram and electrocardiogram employing limb leads I and III (A and B, respectively). The atrial gallop (AG) is clearly seen with each sino-atrial beat and is momentarily absent when a premature ventricular contraction occurs. This illustrates the necessity of an effective presystolic left atrial contraction for the production of this presystolic gallop, although the gallop itself is generated within the left ventricle. The minute heart rate is 73.

audible in the apical region. There were no signs of heart failure. An electrocardiogram revealed tall QRS complexes and the S-T segment and T wave abnormalities characteristic of left ventricular hypertrophy.

A phonocardiogram (Fig. 3) demonstrated the presystolic gallop sound with a fundamental frequency of 40 c.p.s. The presystolic gallop was present in all sino-atrial beats but absent with premature ventricular contractions.

Cardiac catheterization recorded normal pressures within the right side of the heart, including normal pulmonary artery and wedge pressures.

Comment: A ventricular bulge could not be detected through the emphysematous chest. Atrial contraction prior to ventricular systole is necessary for the production of the gallop, as evidenced by absence of the gallop whenever the ventricles contracted prematurely.

In a patient with chronic pulmonary disease the possibility of secondary pulmonary hypertension leading to a right atrial gallop was considered. Normal pulmonary artery pressures ruled this out. The normal pulmonary wedge pressure indicated a normal left atrial pressure. This provides objective evidence that left-sided heart failure was not present. The evidence for left ventricular hypertrophy was electrocardiographic.

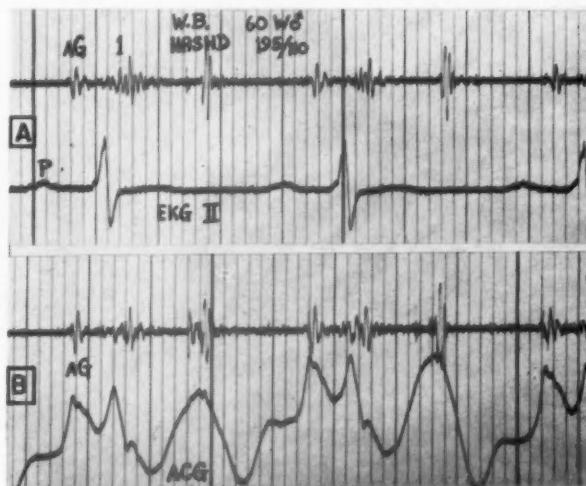


FIG. 4. Case 4. A, simultaneous phonocardiogram and electrocardiogram, lead II. The long P-R interval (0.20 second) and Q-1 interval (0.10 second) result in a wide separation between the atrial gallop (AG) and the first heart sound (AG-1 interval = 0.16 second). This is expressed by equation (2) in the text. B, simultaneous phonocardiogram and apex cardiogram (ACG) demonstrating the prominent forward apical movement with each gallop sound. The minute heart rate is 77.

CASE 4. W. B. was a sixty year old white man who had had hypertension for more than twenty years. During the previous three years he had experienced frequent episodes of angina and suffered two myocardial infarctions. At no time had dyspnea or other evidence of heart failure appeared. The blood pressure was 195/110 mm. Hg. The lungs were clear. Moderate left ventricular hypertrophy was present. A prominent presystolic ventricular bulge was seen and felt at the point of maximum pulsation, followed by a forceful systolic thrust. A loud, low-pitched presystolic gallop sound was audible.

A phonocardiogram (Fig. 4A) showed the loud presystolic gallop with fundamental frequency 50 c.p.s. An apex cardiogram (Fig. 4B) showed the prominent presystolic bulge simultaneous with the onset of the gallop sound.

Comment: Both the gallop bulge and sound were readily evident. Heart failure was never present. Left ventricular hypertrophy was moderate.

CASE 5. R. V. J. was a forty year old white man who, twelve years previously, had experienced an episode of acute glomerulonephritis which progressed to chronic nephritis and renal insufficiency. Several years later hypertension appeared and has been present since. No symptoms of diminished cardiac reserve have appeared. At the time the tracings were recorded, the blood pressure was 160/90 mm. Hg. The

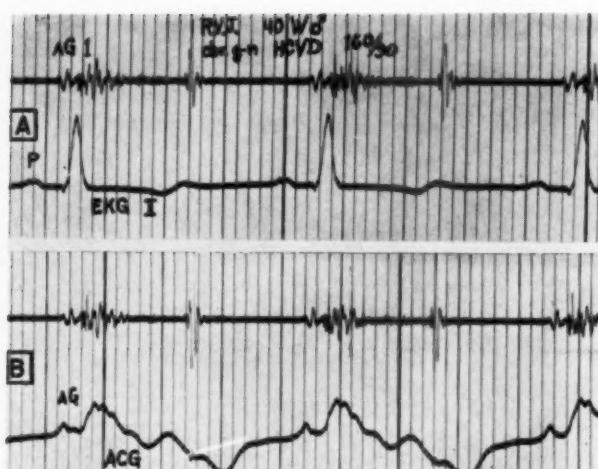


FIG. 5. Case 5. A, simultaneous phonocardiogram and electrocardiogram, lead I. B, simultaneous phonocardiogram and apex cardiogram (ACG). The atrial gallop (AG) sound begins prior to the initial deflection of the QRS complex and is simultaneous with a localized, forward movement recorded on the ACG as a small upward deflection. The minute heart rate is 77.

lungs were clear. There was slight left ventricular hypertrophy. A broad, forceful systolic apical impulse was preceded by a smaller ventricular bulge, which was both visible and palpable. A loud, low-pitched presystolic gallop sound was audible.

A phonocardiogram (Fig. 5A) demonstrated the presystolic gallop sound with a fundamental frequency of 50 c.p.s. A simultaneous apex cardiogram (Fig. 5B) demonstrated a small impulse occurring with the onset of the gallop sound.

Comment: Hypertension in this patient was not of the primary, essential variety but secondary to chronic renal disease. On clinical grounds there was left ventricular hypertrophy but nothing to suggest diminished cardiac reserve. Electrocardiographic evidence of hypertrophy was not present. The presystolic gallop rhythm displayed both mechanical and acoustic features.

Within six months of obtaining the records shown the patient died from renal insufficiency. At postmortem examination the heart demonstrated advanced left ventricular hypertrophy, the thickness of the wall being more than twice the normal thickness. This was far more than suspected clinically. There was no significant dilatation of the ventricles. The atria were non-contributory.

In this patient an atrial gallop persisted for more than six months in the absence of heart failure of any degree.

CASE 6. W. T. was a sixty-three year old Negro man with a documented history of hypertension. He

TABLE II

Investigator	P - AG Interval (sec.)
1. Wolferth and Margolies [12, 13]	0.08-0.14
2. Present study	0.138 (range 0.12-0.17)
3. Frost [11]	0.141 (S.D. 0.023)
4. Weitzman [5]	0.17 (range 0.14-0.24)

was seen for respiratory symptoms secondary to bilateral pleural effusions, which subsequently proved to be of tuberculous origin. The blood pressure was 140/80 mm. Hg. Grade 2 hypertensive retinopathy was present. There were typical signs of pleural effusion posteriorly. There was slight left ventricular hypertrophy. A presystolic ventricular bulge and low-pitched gallop sound were present. The neck veins were flat and there was no edema. Roentgenograms of the chest showed bilateral pleural effusions; there was no pulmonary vascular congestion. The electrocardiogram gave evidence of an old extensive anterior myocardial infarction, no history of which was obtained.

A phonocardiogram (not shown) demonstrated the low-frequency presystolic gallop sound. This sound was essentially unchanged by removal of the intrapleural fluid. The presystolic bulge was recorded on the apex cardiogram.

Comment: This patient had essential hypertension and anatomical left ventricular hypertrophy. An old myocardial infarction was suspected from the electrocardiogram although no history of such an event was elicited. As in Case 2, the blood pressure was normal at the time of recording but the atrial gallop persisted.

COMMENTS

Time Intervals. Vibrations occurring at the time of mechanical atrial contraction have been recorded from the surface of the left atrium via esophageal phonocardiography [7, 8], from within the atrial cavity [9] and from the surface of the chest [5, 10]. These are inaudible to the human ear. The atrial gallop follows these vibrations. One study [5] of time intervals for the left side of the heart indicates that mechanical atrial contraction and its associated vibrations occur 0.10 second after the onset of the P wave. The left atrial gallop begins 0.05 to 0.07 second later. Other values for the time interval between the onset of the P wave and the atrial gallop determined by several investigators and in the present study are listed in Table II. The results of the present study agree closely with

the careful statistical analysis by Frost [11] in seventy-five cases.

In patients with hypertension and left ventricular hypertrophy who are not in heart failure the interval between the beginning of the QRS complex and the first heart sound is prolonged [14]. The present study confirms this observation. (Table III.)

The delayed first heart sound in hypertension is probably secondary to a prolonged period of isometric ventricular contraction in a hypertrophied heart.

The ease with which an atrial gallop sound is heard depends in part upon its separation from the first heart sound ($\Delta G - 1$ interval). This interval is influenced by several variables, as shown by the following:

$$(P - \Delta G) + (\Delta G - 1) = (PQ) + (Q - 1) \quad (1)$$

where $P - \Delta G$ is the interval between onset of the P wave and the atrial gallop (0.14 second).

$\Delta G - 1$ is the interval from the atrial gallop to the first heart sound.

PQ is an alternate notation for the P-R interval of the electrocardiogram.

$Q - 1$ is the interval from the beginning of the QRS complex to the first sound.

Substituting 0.14 second for $P - \Delta G$ and transposing, equation (1) becomes

$$(\Delta G - 1) = (PQ) + (Q - 1) - 0.14 \quad (2)$$

This equation shows that the temporal separation between an atrial gallop and the first heart sound depends principally upon the PQ (P-R) interval and the $Q - 1$ interval. Thus, the prolonged $Q - 1$ interval in hypertensive heart disease facilitates auscultatory recognition of the atrial gallop sound.

Atrial Sounds in Heart Block. Many observers classify the atrial sounds audible in various degrees of A-V block as gallop rhythm. Examination of recorded sounds and time intervals indicates this to be incorrect in most instances. The true atrial gallop sound is of low frequency and occurs approximately 0.14 second after the onset of the P wave. The physiologic fourth heart sound corresponds in time [15] and frequency [16], consisting principally of lower frequencies in the range of 15 to 50 c.p.s. with minimal overtones.

In first degree heart block (prolonged P-R interval) the atrial sound is heard by virtue of the increased P-R interval and occurs at a longer interval after the P wave than true atrial

TABLE III

Investigator	Patient Group	Q-1 Interval (sec.)
Weissler, Leonard and Warren [14] Weissler, Leonard and Warren [14]	Normal (18 cases) Hypertension with left ventricular hypertrophy but without heart failure Hypertension with left ventricular hypertrophy but without heart failure (Cases 1-6)	0.055* 0.07 0.072
Present study		

* Standard deviation 0.01.

gallop. In acute rheumatic fever decreasing a prolonged P-R interval with atropine will cause this atrial component to merge with the soft first heart sound and restore the normal intensity of the latter.

In second degree heart block (incomplete A-V block with non-conducted beats) atrial sounds are audible following the non-conducted P waves. The time interval from a blocked P wave to the following atrial sound is equal to or slightly greater than the interval from a conducted P wave to the ensuing first heart sound [17].

With complete heart block two audible atrial sounds may occur and have been recorded [18]. The inaudible vibrations of mechanical atrial contraction precede both of these sounds. The first audible sound follows the P wave by 0.12 to 0.15 second and in time corresponds to the fourth heart sound or the true atrial gallop. The second audible sound occurs 0.22 to 0.26 second after the P wave and corresponds to the atrial sounds often heard when the P-R interval is prolonged or in second degree heart block following a non-conducted P wave.

The atrial sounds occurring with various types of A-V block usually appear on sound records as high-frequency tones compared to atrial gallop. This implies a different mechanism of production.

True gallop originates in the ventricle and is associated with a ventricular bulge. No bulge or ballistic thrust toward the right shoulder has been demonstrated at the time of atrial sounds in heart block.

When complete A-V block is present atrial sounds occur in systole as well as in diastole. During ventricular systole the A-V valves are closed. It is difficult to imagine the atrial sound heard during ventricular systole as originating

TABLE IV

Case No.	Patient	Group	Heart Rate (beats/min.)	2-vG Interval * (sec.)	Fundamental Frequency of Gallop Sound (c.p.s.)
7	G. W.	Mitral insufficiency	67	0.10	40
8	G. W. D.	Mitral insufficiency	58	0.10	40
9	M. C. D.	Mitral insufficiency	94	0.10	50-60
10	A. L.	Aortic insufficiency	57	0.14	30-40
11	J. E. T.	Heart failure	80	0.15	30-40
12	H. K.	Heart failure	75	0.14	35
13	E. C.	Heart failure	84	0.16	25
14	W. O. H.	Heart failure	96	0.16	35

* 2-vG interval is the time from the start of the second heart sound to the start of the rapid ventricular filling gallop.

from within the ventricle, as is the case for true gallop.

At the present time it does not appear justified to consider all sounds resulting from atrial contraction as atrial gallops. Clearly, further knowledge concerning the mechanisms of such sounds is necessary for valid classification.

Clinical Significance. Presystolic gallop of the left side of the heart occurs frequently in essential hypertension, and when present in this disease invariably indicates left ventricular hypertrophy [5]. The same is true for secondary hypertension, as occurs with renal disease. The present observations support this correlation. In all eight patients with atrial gallop and hypertensive disease there was evidence of left ventricular hypertrophy, either from physical examination, roentgenograms and/or the electrocardiogram. Therefore, an atrial gallop in the presence of hypertension warrants a diagnosis of hypertensive heart disease.

The significance of atrial gallop in aortic valve disease is not known but we may infer that here, too, ventricular hypertrophy exists when atrial gallop is present. In systemic vascular hypertension, aortic stenosis and aortic insufficiency with resultant systolic hypertension there is a state of left ventricular systolic overload. We may suspect that the evolution of atrial gallop in these situations is as follows:

systolic overload → ventricular hypertrophy
→ presystolic gallop

This hypothesis is also applicable to the right side of the heart. Right atrial gallops occur in primary pulmonary hypertension, secondary pulmonary hypertension of varied etiology and in pulmonic stenosis.

The audible atrial presystolic gallop is not the sound of atrial contraction *per se*, but is generated within the hypertrophied ventricle. Nevertheless, an effective atrial contraction is necessary for the production of this presystolic sound. It is not heard in atrial fibrillation and is temporarily absent prior to a premature ventricular contraction. Presystolic gallop may be present for years and is of no immediate prognostic value [19]. In the present study all patients with atrial gallop alone showed no evidence of heart failure. It appears that presystolic gallop does not necessarily imply a decompensated state.

RAPID FILLING GALLOP

Observations

Rapid filling gallops were recorded in eight patients—three with rheumatic mitral insufficiency, one with rheumatic aortic insufficiency, and four with heart failure secondary to hypertensive and/or arteriosclerotic heart disease. Time intervals for these eight patients are shown in Table IV. In six of these the rapid filling gallop was the only extra heart sound. Two patients (Cases 13 and 14) had both rapid filling and atrial gallops, as previously mentioned; they are described in detail elsewhere [6].

CASE 7. C. W., a thirty-eight year old Negro man, was seen because of gastrointestinal complaints. There was no history of rheumatic fever and no cardiopulmonary symptoms.

The blood pressure and pulse were normal. The lungs were clear. The heart did not appear enlarged. A fine apical systolic thrill and loud, harsh, holosystolic murmur were present. The second sound was followed by a loud, low-pitched gallop sound and apical bulge. Diastole was otherwise silent.

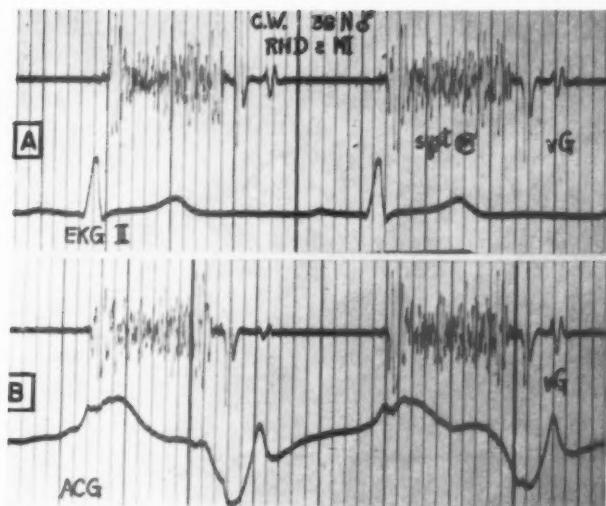


FIG. 6. Case 7. A, simultaneous phonocardiogram and electrocardiogram, lead II. B, simultaneous phonocardiogram and apex cardiogram (ACG). The holosystolic murmur of mitral insufficiency is recorded. There is no diastolic murmur. A rapid ventricular filling gallop (vG) is seen in early diastole and is represented by a low-frequency sound and an apical bulge, the latter recorded as a sharp upward deflection on the apex cardiogram. The minute heart rate is 67.

Fluoroscopy revealed slight left ventricular enlargement. The electrocardiogram showed tall QRS complexes over the left precordium.

A phonocardiogram (Fig. 6A) recorded the holosystolic murmur and an early diastolic sound of low frequency (fundamental 40 c.p.s.). The apex cardiogram (Fig. 6B) showed an upward deflection simultaneous with the low-pitched sound.

Comment: The low fundamental frequency of the early diastolic sound is not consistent with the opening snap of a stenotic mitral valve and suggests gallop rhythm as the underlying mechanism. The simultaneous apical thrust confirms the presence of gallop rhythm and rules out mitral stenosis. There was no heart failure.

CASE 8. G. W. D., a twenty-seven year old white man, was seen for interim evaluation of rheumatic heart disease. There was a good past history of rheumatic fever. During military service a diagnosis of rheumatic heart disease was made. The patient was experiencing moderate exertional dyspnea. There was no orthopnea or paroxysmal nocturnal dyspnea.

The blood pressure and pulse were normal. The neck veins were flat and the lungs clear. The heart was slightly enlarged. A loud apical systolic murmur was audible. The second pulmonic sound was accentuated. At the apex a low-pitched early diastolic sound was present, associated with a prominent localized ventricular diastolic thrust. There was no

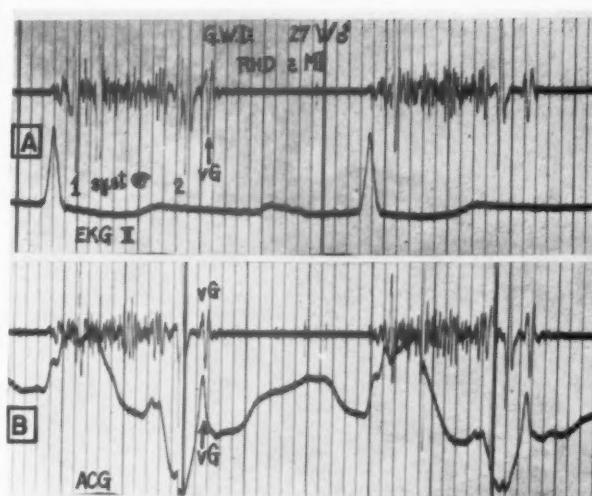


FIG. 7. Case 8. A, simultaneous phonocardiogram and electrocardiogram, lead II. B, simultaneous phonocardiogram and apex cardiogram (ACG). The holosystolic murmur of mitral insufficiency is recorded. There is no diastolic murmur. A rapid ventricular filling gallop (vG) occurs in early diastole. Both the gallop sound and apical bulge are recorded. The minute heart rate is 58.

edema or other signs of congestive heart failure. The electrocardiogram was within normal limits.

The phonocardiogram (Fig. 7A) showed the systolic murmur and a high amplitude low-frequency (fundamental 40 c.p.s.) sound in early diastole. The apex cardiogram (Fig. 7B) demonstrated the rapid upward deflection caused by an outward ventricular thrust simultaneous with this sound.

Comment: The low frequency of the diastolic sound and a simultaneous ventricular bulge are indicative of gallop rhythm and exclude mitral stenosis. Heart failure was not present.

CASE 9. M. C. D., a thirty-five year old white man, was seen because of increasing severity of cardio-pulmonary symptoms. An episode of acute rheumatic fever had occurred at the age of ten. Between the ages twenty and twenty-five the patient first noted exertional dyspnea, which gradually progressed with the appearance of orthopnea.

At the age of thirty-four, nine months before study, the patient was evaluated for mitral valve surgery. The heart was moderately enlarged. The rhythm was regular sinus. Apical systolic and diastolic thrills and murmurs were present. Gallop rhythm was not observed. There was roentgenographic evidence of marked left atrial enlargement. The electrocardiogram showed a P mitrale, incomplete right bundle branch block, and was suggestive of right ventricular hypertrophy. Left heart catheterization demonstrated an end diastolic pressure gradient across the mitral valve of 20 mm. Hg. Mitral commissurotomy was

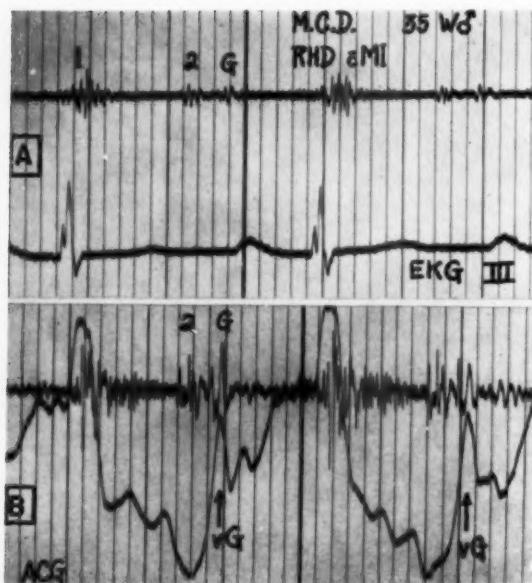


FIG. 8. Case 9. A, simultaneous low-volume phonocardiogram and electrocardiogram, lead III. The gallop sound (G) is clearly seen and occurs 0.10 second after the second heart sound. B, simultaneous phonocardiogram and apex cardiogram (ACG). Systolic and diastolic murmurs are seen. The gallop sound (G) occurs simultaneous with a prominent forward movement (vG) localized to the apical region. The minute heart rate is 94.

performed; both stenosis and insufficiency were found at surgery. The stenosis alone was alleviated.

The patient continued to experience increasing dyspnea and marked orthopnea, which prompted his rehospitalization. The blood pressure was 110/70 mm. Hg. The pulse was 90 and regular. Occasional moist rales were present at the lung bases. The heart was enlarged, almost reaching the anterior axillary line. Apical systolic and diastolic thrills and murmurs were present. A low-pitched sound was audible in early diastole and associated with a prominent ventricular bulge. The electrocardiogram was essentially unchanged since surgery nine months previously. Chest roentgenograms confirmed the increased cardiomegaly and showed a giant left atrium.

A phonocardiogram (Fig. 8A) recorded the apical systolic and diastolic murmurs and the early diastolic sound of low frequency (fundamental 50 to 60 c.p.s.) simultaneous with a sharp upward deflection on the apex cardiogram. (Fig. 8B.)

Comment: Mitral stenosis had been corrected nine months previously, at which time mitral insufficiency was confirmed. It is possible that valvular surgery increased the degree of insufficiency. Certainly, relief of the stenosis alone would permit an increase in ventricular filling and hence the volume of regurgitation with each systole. The mechanism of gallop produced by severe mitral insufficiency was further

enhanced by the appearance of early left ventricular failure.

Mitral insufficiency was certainly the major valvular lesion at the time of recording. A mitral diastolic thrill and murmur were present, but this may occur with mitral valve deformity and severe insufficiency without stenosis of hemodynamic importance.

CASE 10. A. L., a twenty-seven year old white female housewife and mother, was seen at intervals for asymptomatic rheumatic heart disease with aortic insufficiency. Normal sinus rhythm was present. The blood pressure was 140/50 mm. Hg with sounds audible down to 20 mm. There was slight left ventricular hypertrophy and a blowing aortic diastolic murmur of medium intensity. At the apex a low-pitched sound occurred in early diastole and a corresponding apical inflection could be seen.

A phonocardiogram (Fig. 9) showed a low-frequency (fundamental 30 to 40 c.p.s.) sound occurring 0.14 second after the onset of the second heart sound.

Comment: The low fundamental frequency of the extra sound, its interval from the second heart sound, and the corresponding forward apical movement indicate that this was a gallop sound and not an opening mitral snap. There is no evidence of mitral valve disease in this patient. Unfortunately, the apex cardiogram was not recorded.

CASE 11. J. E. T., a fifty-seven year old Negro man, was seen because of increasing dyspnea and edema of the ankles. The patient had a long history of hypertension. When first seen, four years previously, he had symptoms of congestive heart failure. Atrial fibrillation was present. He had been treated with digitalis, sodium restriction and diuretics. Heart failure was constantly present to varying degrees.

The blood pressure was 160/110 mm. Hg. The rhythm was atrial fibrillation with a ventricular rate of 80. There was grade 2 hypertensive retinopathy. Fine moist rales were heard at both lung bases. The heart was enlarged beyond the anterior axillary line. A soft apical systolic murmur and soft high-pitched aortic diastolic murmur were audible. A prominent low-pitched sound in early diastole was heard over the left precordium near the anterior axillary line. A corresponding ventricular bulge was seen and felt in the area of maximum cardiac pulsation. There was 1-plus pitting edema of the ankles.

A roentgenogram of the chest demonstrated cardiomegaly, pulmonary congestion and a widely dilated, tortuous aorta. The venous pressure was 260 mm. saline.

The phonocardiogram (Fig. 10B) recorded the early diastolic low-frequency (fundamental 30 to

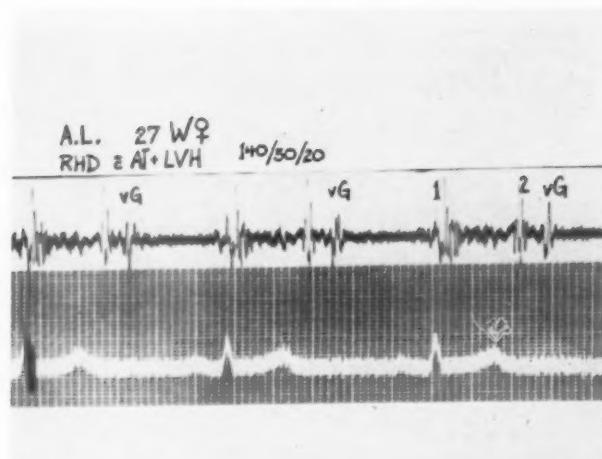


FIG. 9. Case 10. Simultaneous phonocardiogram and electrocardiogram. A slight amount of noise is present throughout the sound record. The rapid ventricular filling gallop sound (vG) is of low fundamental frequency. This is best appreciated in the last cycle shown. The minute heart rate is 57.

40 c.p.s.) gallop sound simultaneous with the upward deflection on the apex recording caused by the ventricular bulge. (Fig. 10A.)

Comment: Atrial fibrillation precluded the presence of an atrial gallop in this hypertensive patient. The rapid ventricular filling phase of early diastole is a passive phenomenon and begins upon opening of the A-V valves, even in the presence of a variety of disturbances of rhythm and conduction. The rapid filling gallop is, therefore, temporally related to the opening of the A-V valve(s).

The aortic diastolic murmur in this case represented "dynamic" aortic insufficiency, i.e., aortic valvular incompetency resulting from hypertensive dilatation of the valve ring and base of the aorta. In this patient aortic incompetency appeared to be of minor degree. Peripheral signs were absent and the diastolic blood pressure was well maintained. The apical systolic murmur was typical of "relative" mitral insufficiency secondary to ventricular enlargement.

In this patient left ventricular failure was the major factor in the production of gallop rhythm. Minor degrees of aortic and mitral incompetency may have had an additive effect.

CASE 12. H. K. was a fifty-six year old white man with diabetes mellitus of long duration who was seen because of recurrent symptoms of congestive heart failure. There was a past history of a questionable myocardial infarction.

APRIL, 1960

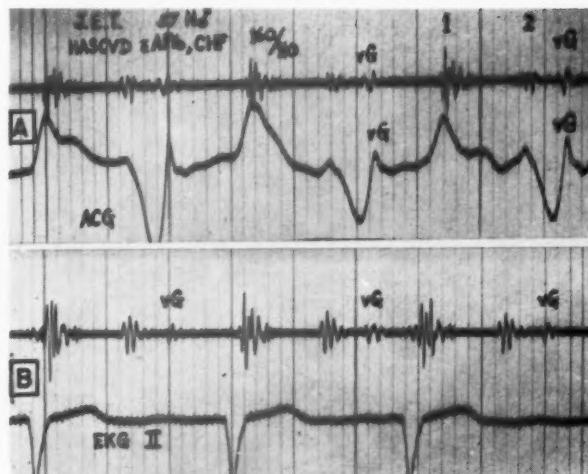


FIG. 10. Case 11. A, simultaneous phonocardiogram and apex cardiogram (ACG). The rapid ventricular filling gallop (vG) is represented by both a localized bulge in the apical region and a sound occurring 0.15 second after the second heart sound. B, simultaneous phonocardiogram and electrocardiogram, lead II. The rhythm is atrial fibrillation with a minute ventricular rate of 80.

Physical examination revealed a normal blood pressure and pulse. There was marked obesity of the trunk and 4-plus pitting edema of the legs and ankles. There were occasional moist basilar rales. The heart was enlarged to the anterior axillary line. A soft low-pitched sound was heard in early diastole near the apex. A corresponding ventricular movement was not transmitted through the obese chest wall. The electrocardiogram showed complete left bundle branch block.

A phonocardiogram (not shown) recorded the low-frequency (fundamental 35 c.p.s.) gallop sound.

Comment: The clinical diagnosis was diabetes mellitus and arteriosclerotic heart disease with congestive heart failure, left bundle branch block and questionable old myocardial infarction.

Galloping rhythm resulted from heart failure. Obesity of the chest wall prevented detection of a corresponding ventricular thrust.

COMMENT

The rapid ventricular filling gallop, or briefly ventricular gallop, is regarded as the pathologic counterpart of the physiologic third heart sound. Important similarities confirm this view; certain dissimilarities aid in the differential diagnosis between them.

Time Intervals. The physiologic third heart sound and the ventricular gallop occur at the same time in the cardiac cycle, this being the latter portion of the rapid ventricular filling

TABLE V

Investigator	Interval Measured*	Duration of Interval (sec.)	
		Mean Value	Range
1. McKee [75]	2-3	0.11-0.15
2. Dock, Grandell and Taubman [3]	2-3	0.147	0.12-0.18
3. Frost [11]	2-3 and 2-vG	0.145	0.10-0.20
4. Wolferth and Margolies [12]	2-3 and 2-vG	0.13-0.18
5. Present study (heart failure group)	2-vG	0.15	0.14-0.16
6. Present study (mitral insufficiency group)	2-vG	0.10	0.10

* 2-3 interval is the time from the start of the second heart sound to the start of the physiologic third heart sound.
2-vG interval is the time from the start of the second heart sound to the start of the rapid ventricular filling gallop.

period. Rapid filling begins upon opening of the A-V valve(s). The rate of rapid filling and the duration of this period are relatively independent of heart rate. Thus, the third heart sound and ventricular gallop bear a constant relation to opening of the A-V valve and their timing does not correlate with the heart rate [11].

When isometric ventricular relaxation is of normal duration the third heart sound and ventricular gallop bear a constant relation to the second heart sound, which is the reference sound employed in phonocardiography. Time intervals between the second heart sound and the third heart sound or ventricular gallop are listed in Table V. When determined, mean values (investigators 2, 3 and 5 in Table V) for the interval between the second heart sound and third heart sound (2-3 interval) or ventricular gallop (2-vG interval) agree closely. The statistical analysis by Frost [11] showed no significant difference in timing between the physiologic third heart sound and ventricular gallop in either males or females or between the two sexes. Other investigators [12] also found no difference in timing between the third heart sound and ventricular gallop.

The time of ventricular gallop in mitral insufficiency is a special case. In rheumatic mitral valve disease left atrial pressure is elevated, resulting in earlier opening of the mitral valve, ending a shortened period of isometric ventricular relaxation. In mitral stenosis the interval between the second heart sound and the mitral opening snap (2-OS interval) is an index of left atrial pressure, shorter 2-OS intervals being roughly correlated with higher atrial pressures. In mitral insufficiency with elevated atrial

pressure the mitral valve opens earlier. Since rapid filling gallop is temporally related to opening of the A-V valve, this gallop will occur earlier in mitral insufficiency, as shown by our three cases (investigator 6, Table V).

Frequency of Sounds. The range of fundamental frequencies for both the physiologic third heart sound and ventricular gallop are identical, and supports the view that the mechanism of sound production is similar. This frequency range is 20 to 50 c.p.s. [15,16]. In the present study this range was approximately 25 to 50 c.p.s.

Mechanical Features. The ventricular movements and forces associated with the third heart sound and rapid filling gallop are qualitatively similar, but differ quantitatively. Only with the loudest third heart sounds are these movements and forces prominent and of the magnitude seen with the least intense gallops [4]. A ventricular thrust must possess ample force to be detectable at the surface of the chest wall. Therefore, an outward precordial movement simultaneous with an early diastolic sound of low frequency indicates gallop rhythm and makes the presence of a physiologic third heart sound unlikely. The converse is not true, for thick chest walls often prevent transmission of recognizable gallop movements to the chest surface.

Factors in the Production of Gallop Rhythm. Ventricular gallop rhythm occurs when there is an abnormal relation between the rate of rapid ventricular filling and the ventricle's ability to accommodate its increasing volume. The wave of rapid left ventricular filling is increased in mitral insufficiency, in which the left atrial volume is

large, the atrial pressure high and mitral stenosis not of a degree to restrain the rate of flow from atrium to ventricle. Indeed, ventricular gallop in the presence of mitral insufficiency is a frequent finding. In thirty patients with mitral insufficiency ventricular gallop was heard in 50 per cent and the associated thrust was often seen and felt [20]. In acute rheumatic carditis with mitral incompetence the third heart sound is accentuated [21] or true gallop may occur.

In aortic insufficiency the regurgitant blood stream augments ventricular filling and the total rapid filling wave exceeds that normally present. This may result in ventricular gallop.

Left-to-right shunts at the left ventricular level or between the great vessels result in increased left ventricular diastolic filling and stroke volume. Examples are interventricular septal defect, patent ductus arteriosus and aortic pulmonary window. Interatrial septal defect increases diastolic filling of the right ventricle and rapid filling gallop of the right ventricle may occur.

More common than ventricular gallop due to an increased filling wave is ventricular gallop due to abnormal accommodation during the volume changes of diastole. The usual underlying condition in this situation is heart failure, in which myocardial tone is poor. Ventricular gallop may appear as a sign of incipient or early heart failure and is virtually pathognomonic of heart failure when one can rule out causes of a significant increase in the filling wave, such as organic valvular insufficiency and shunts.

The balance between filling and accommodation is affected by changes in venous return. Venous occlusive cuffs applied to the extremities will reduce the intensity of the third heart sound [22] and ventricular gallop sound and magnitude of the apical gallop thrust [23]. A similar response may be produced by other technics for pooling venous blood, such as sitting with the legs dependent, standing or pharmacologic ganglionic blockade.

The question of which specific cardiac structures produce the gallop sound is presently unsettled. One view holds that the myocardium generates the sound at the time of abnormal bulging or distention. The other major hypothesis considers the sound to be of valvular origin. This concept is supported by the ease with which valvular structures are set into vibration and produce sound. Also, one patient

has been observed in whom rapid filling gallop of the right ventricle occurred only when right ventricular pressure momentarily exceeded right atrial pressure during early diastole. Momentary closure of the tricuspid valve was postulated and considered responsible for the gallop sound [24]. Another study demonstrated atrial pressure greater than ventricular pressure at the time of gallop [25]. This would refute the theory that gallop sounds result from momentary closure of A-V valves. Further information is certainly necessary for a definitive answer to this question.

Differential Diagnosis. The rapid filling gallop sound must be distinguished from other sounds occurring in early diastole, namely, a split second sound, the opening mitral snap, vibrations in constrictive pericarditis and the physiologic third heart sound. Of singular importance is the localized surface precordial bulge or thrust, which only occurs with gallop and may be distinguished from the usually diffuse shock occurring with constrictive pericarditis.

The earlier timing of ventricular gallop in mitral valve disease may result in the erroneous designation of this sound as an opening mitral snap [26]. The ventricular gallop sound is lower pitched, its intensity is diminished by venous pooling and the systolic murmur of mitral insufficiency is heard. When a localized precordial bulge occurs with the sound the diagnosis is certain and mitral insufficiency is the predominant valve lesion.

In predominant mitral stenosis rapid filling gallop of the left ventricle does not occur, but it may be generated from the right ventricle by tricuspid incompetence or right ventricular failure.

Clinical Significance. It appears that rapid filling gallop implies diastolic overload of the ventricle. It is not necessarily related to ultimate prognosis and may be present in curable heart disease such as occurs with beriberi and thyrotoxicosis. In one hundred patients with heart disease there was no correlation between the clinical state after two to three years and the presence or absence of gallop at the time of initial evaluation [19]. Our experience agrees with this conclusion.

SYSTOLIC SOUNDS

In the present study systolic sounds of any nature are not classified as gallops. The following two examples illustrate the normal apex cardiogram.

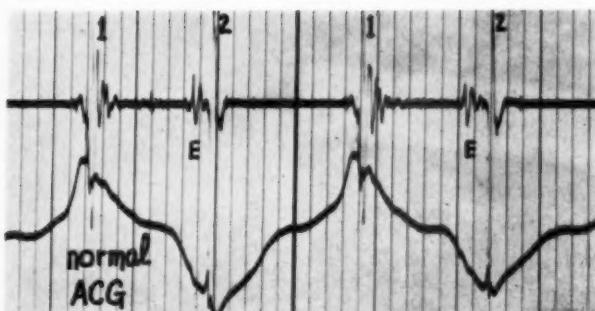


FIG. 11. Case 20. Simultaneous phonocardiogram and apex cardiogram (ACG). An extra heart sound (E) occurs in late systole and is not associated with any abnormality of the apex cardiogram. The minute heart rate is 88.

CASE 20. J. R. was a thirty-five year old Negro man with no symptoms of cardiovascular disease. The phonocardiogram showed a late systolic sound of low frequency. (Fig. 11.)

The apex cardiogram was normal. Following the second heart sound there was a gradual forward movement as ventricular filling occurred. At the onset of ventricular contraction there was a sudden increase in the rate of forward movement, which resulted in the maximum palpable cardiac impulse.

Comment: An additional heart sound in systole is often of unknown etiology and of no clinical significance [27], in which case it is not associated with any abnormality of ventricular dynamics.

CASE 21. A. C. was a sixty-nine year old Negro man with previously documented tertiary syphilis and aortic insufficiency. He was seen because of the recent appearance of exertional dyspnea, mild orthopnea and swelling of the ankles. Physical examination revealed a blood pressure of 190/90 mm. Hg and collapsing pulses; a pistol shot was elicited over major arteries. The heart was moderately enlarged. A loud aortic diastolic murmur radiated down the left sternal border. A high-pitched early systolic sound was audible over the aortic area and was immediately followed by a harsh systolic murmur which radiated to the vessels of the neck.

The electrocardiogram showed left axis deviation of QRS. There was electrocardiographic evidence of left ventricular hypertrophy with large amplitude QRS complexes and abnormalities of the S-T segment and T wave. The serological test for syphilis was positive, as previously. The clinical diagnosis was syphilitic aortic insufficiency of moderate degree with congestive heart failure.

The phonocardiogram (Fig. 12A) demonstrated a sound with many high frequency components, beginning 0.06 second after the onset of the first heart sound. The apex cardiogram (Fig. 12B) was

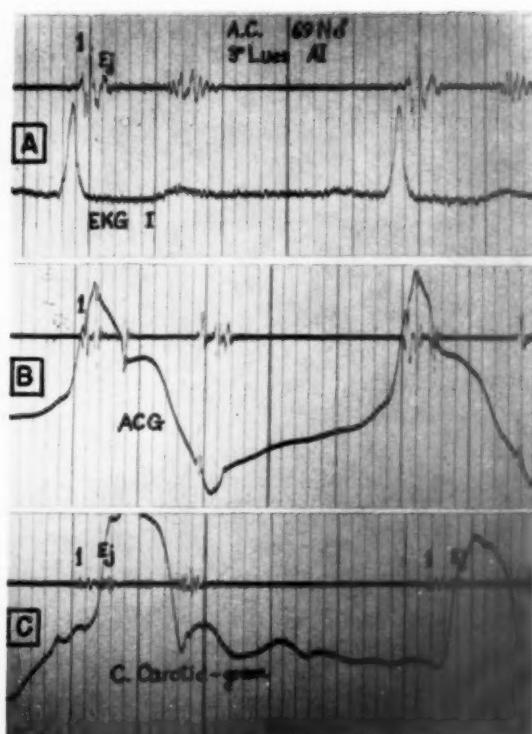


FIG. 12. Case 21. A, simultaneous phonocardiogram at the heart base and electrocardiogram, lead I. Following the first heart sound there is an aortic ejection sound (Ej). B, simultaneous phonocardiogram and apex cardiogram. The apex movement is normal. The rapid forward systolic movement of the apex is simultaneous with the onset of the first heart sound and precedes the aortic ejection sound. C, simultaneous phonocardiogram and an externally recorded common carotid pulse. The systolic expansion of this vessel occurs simultaneous with the ejection sound (Ej).

normal and the start of the maximum impulse preceded the first heart sound. A common carotid artery pulse was recorded externally (Fig. 12C) and demonstrated the systolic distention of this vessel to occur simultaneous with the onset of the high-frequency systolic sound. This supports the view that this sound was the result of vascular vibrations in the great vessels initiated by ejection.

Comment: Insufficiency of a semilunar valve results in early systolic vascular vibrations at the time of ejection. Increased stroke volume and a dilated great vessel above the valve [28] are believed to be the important factors in the production of this sound.

In stenosis of a semilunar valve an early systolic vascular vibration may be audible, presumably the result of a narrow jet-like ejection stream entering the great vessel with increased velocity.

Early ejection sounds are generated by the right side of the heart in pulmonic insufficiency,

idiopathic dilatation of the pulmonary artery and pulmonic stenosis, and from the left side of the heart in aortic insufficiency or stenosis. These systolic sounds are generally of high frequency. A localized ventricular bulge simultaneous with the sound is not demonstrable. These sounds fulfill none of the criteria for gallop rhythm.

SUMMARY

Gallop rhythm is a mechanical event associated with a relatively rapid rate of ventricular filling and characterized by a ventricular bulge and a low-frequency sound. Relatively rapid ventricular filling occurs during two divisions of diastole: (1) the rapid filling period, which follows opening of the A-V valves, and (2) the period of atrial contraction. Therefore, two types of gallop exist and are named rapid filling (or ventricular) gallop and atrial gallop, respectively. Both are diastolic in timing. Systolic sounds are not gallop sounds and must be otherwise named.

Either gallop may occur at any heart rate.

Fourteen patients with gallop rhythm were studied. Of these, six showed atrial gallop alone, six showed rapid filling gallop alone, and two showed both types of gallop in every cardiac cycle.

Left atrial gallop occurs 0.14 second after the onset of the P wave.

Atrial gallop is of no prognostic significance and is not related to heart failure. Atrial gallop is often generated within a hypertrophied ventricle which has been subjected to systolic overload.

Rapid filling or ventricular gallop occurs 0.15 second after the second heart sound. In the special case of mitral insufficiency this gallop occurs earlier for reasons explained.

Rapid filling gallop occurs when there is an imbalance between the wave of rapid ventricular filling and the ventricle's ability to accommodate its increasing diastolic volume. An increased filling wave results from valvular insufficiency and cardiovascular shunts. Abnormal ventricular accommodation occurs in heart failure, in which myocardial tone is poor.

Rapid filling gallop indicates ventricular diastolic overload. The prognosis is that of the underlying disease and does not correlate with the presence or absence of gallop.

Systolic sounds of any nature are excluded from the category of gallop, as defined herein.

Acknowledgment: I am indebted to Dr. C. E. Kossmann for his criticisms in the preparation of this manuscript.

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Clinicopathologic Conference

Inferior Vena Caval Occlusion

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Harroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A FIFTY-SIX year old white housewife (C. J.) was admitted to the Barnes Hospital for the second time on April 18, 1959. She died on June 6, 1959.

The patient's first admission to the Barnes Hospital, from September 22, 1958 to October 11, 1958, was for ulcers of the leg of twenty years' duration.

In 1928, during the first of her three full term pregnancies, the patient noted swelling of her legs, particularly the left, which also became "purple from the ankle down." The latter was diagnosed as "rheumatic purpura." Except for "anemia," the pregnancy was uncomplicated. Swelling of her legs was severe during subsequent pregnancies. In 1938 "ulcers" appeared about her ankles. They were said to be secondary to varicose veins and continued intermittently together with the swelling of her legs until, nine years prior to the first admission, she had "the veins tied in the groin." Abdominal varicose veins were noted at this time. The venous ligations proved to be of only temporary help and one year later the patient underwent "sympathectomy." The swelling and ulcers of the leg were subsequently more constant, finally necessitating bilateral vein stripping in 1956. In February 1957, she was hospitalized for four weeks because of cough, pleuritic-like pain in the chest, fever and chills. She was told that she had "pneumonia," was given several blood transfusions and a number of medications, including some "antibiotics." There had been no recognized blood loss. While confined in the hospital, the patient continued to have episodes of swelling of the legs bilaterally. After her discharge, she continued to be "anemic," requiring twenty-nine blood transfusions during the next fifteen months, five months prior to this admission she was told that she was no longer "anemic."

One year prior to this admission she noted the onset of vague, generalized abdominal distress, unassociated with nausea, vomiting, melena, diarrhea or alteration in her chronic state of constipation. Eating tended to aggravate the abdominal distress. All studies were said to be within normal limits. A bland diet caused complete relief of her symptoms.

Nine months prior to admission to the Barnes Hospital, the patient was again hospitalized for "pneumonia." She subsequently noticed dyspnea on exertion and edema of the ankles. The edema increased to massive proportions during the following three months and was associated with abdominal swelling. There was no history of frank shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, palpitation or chest pain. At this time the patient was given several injections of a mercurial diuretic and an unknown pill was administered daily; there was some relief of her complaints. During the five months prior to this admission, the patient had noted progression in the severity of her dyspnea, dry cough and pleuritic-like chest pain, with persistence of bilateral ulcers and edema of her legs, the left being more severely involved. For four weeks she had occasionally had chills and fever.

Her usual weight was 120 pounds; at the time of admission she weighed 132 pounds.

The patient thought she was allergic to penicillin. She described many recurrent episodes of fever, dysuria, urgency and frequency during the previous thirty years. Decreased hearing acuity bilaterally was ascribed to bilateral infection of the ear. Menstrual history revealed normal, although irregular periods until their cessation two years previously.

The patient's mother (eighty-nine years old) had diabetes, hypertension and "heart trouble";

her father died (sixty-two years) of "uremic poisoning," and two of her five siblings have "gallstones."

On physical examination the blood pressure was 110/80 mm. Hg, pulse 88, respirations 16, and temperature 36.8°C. The patient was a cachectic, white woman who appeared older than her stated age of fifty-six. There was pitting edema of both lower extremities, 1 plus on the right, 3 plus on the left, and a 4 by 6 cm. superficial ulceration over both lateral malleoli, the latter being surrounded by an area of inflammation. Massively dilated abdominal and posterior thoracic collateral venous circulation was present with an inferior to superior direction of flow. One observer noted lid lag bilaterally as well as the presence of a palpable, although not enlarged thyroid. The neck was supple and there was no venous distention. Several firm, non-tender, movable 3 by 4 cm. lymph nodes were felt in each axilla, with several firm, movable to semi-fixed nodes in the submaxillary and inguinal areas. The chest was increased in antero-posterior diameter; an area of decreased breath sounds was described at the base of the right lung by one observer. The left border of cardiac dullness was 9 cm. to the left of the midsternal line in the fifth interspace; heart sounds were of fair quality, with marked increase in the intensity of both the first mitral and second pulmonic heart sounds. A harsh systolic grade 2 to 4 murmur was heard in the apical area and did not radiate. Peripheral pulsations were normal. The firm, slightly tender liver was palpated 3 cm. below the right costal margin. The abdomen was soft; there was no evidence of ascites. No costovertebral angle tenderness was detected. The neurological examination was physiologic.

The laboratory data were as follows: The white blood cell count was 4,850 per cu. mm. with 59 per cent segmented forms, 35 per cent lymphocytes and 6 per cent monocytes; packed red cell volume was 37 per cent; hemoglobin, 13.7 gm. per cent; the platelets appeared to be adequate in number and the red blood cell morphology was described as being normal. The urine specific gravity was 1.020, pH 5, protein trace, with a negative sugar reaction; 8 to 10 red blood cells per high power field and occasional white blood cells were found in the centrifuged sediment. The blood cardiolipin test for syphilis was negative. Four stool specimens were negative for occult blood and neutral

fat. The blood non-protein nitrogen was 29 mg. per cent, fasting blood sugar 68 mg. per cent, serum cholesterol 134 mg. per cent, uric acid 5.1 mg. per cent, calcium 10.8 mg. per cent, phosphorus 4.6 mg. per cent, alkaline phosphatase 10.9 Bodansky units (repeat value was 10.6 Bodansky units), albumin 2.8 gm. per cent, globulin 4.4 gm. per cent, cephalin cholesterol flocculation 1 plus, thymol turbidity 14.1 units, total serum bilirubin less than 0.8 mg. per cent. Serum glutamic oxaloacetic transaminase was 193 units and serum glutamic pyruvic transaminase was greater than 100 units. The prothrombin time was reported as being 80 per cent of the normal value. The Diagnex® Blue test was reported as greater than 0.6 mg. The Sia water test was negative on two occasions, as was the cryoglobulin precipitation test. An electrocardiogram was within normal limits. Radiographic examinations of the chest and upper and lower gastrointestinal tract revealed some atelectasis and old fibrosis of the lower lobe of the left lung with old pleural scarring at the base of the right lung; minimal scoliosis of dorsal spine; moderate splenomegaly; compression fracture of the third lumbar vertebra with degenerative osteoarthritis; multiple Cushing clips; no abnormalities of the entire gastrointestinal tract.

During the initial week, the patient remained unchanged clinically. Repeat hemograms merely confirmed the results of the studies carried out on admission, and the platelet counts approximated 220,000 per cu. mm. Many white blood cells were found in several urine specimens and culture of a clean voided specimen grew a moderate growth of *Aerobacter aerogenes*. A surgical consultant described "severe stasis disease . . . with development of abdominal venous collaterals." An axillary lymph node biopsy was performed; no diagnosis was made on pathological examination. At about this time, an alteration was discovered in the values of the liver profile tests made on admission. The cephalin cholesterol flocculation was 4 plus, thymol turbidity 19.5 units, alkaline phosphatase 10.6 mg. per cent, bilirubin less than 0.8 mg. per cent. On October 3 a differential glucose tolerance test was performed, utilizing a peripheral extremity vein and an abdominal collateral. The fasting blood sugar was 77 mg. per cent with samples from the collateral circulation being 104 mg. per cent (fifteen minutes), 121 mg. per cent (thirty minutes) and 159 mg. per cent

(forty-seven minutes) while those from the peripheral vein were 133 mg. per cent (twenty minutes) and 152 mg. per cent (forty minutes). A needle biopsy of the liver was performed uneventfully; the pathological diagnosis of the specimen was "hemosiderosis." Electrophoretic analysis of the patient's serum showed a non-specific increase in the gamma globulins. With general supportive care, the patient seemed to improve. One observer thought there was a definite regression in the size of the liver; splenomegaly remained a radiographic diagnosis. The hemogram at the time of discharge was essentially unchanged.

The second admission to the Barnes Hospital was from April 18 to June 9, 1959. The patient did very well and remained active until three months prior to this admission when she began to have intermittent episodes of vomiting (bile) and associated watery diarrhea (seven to eight times daily). These episodes almost invariably followed the ingestion of fatty food. She had noted progressive loss in tissue weight and a concomitant gain in edema weight, with the development of extreme weakness, incapacitating shortness of breath on the most minimal exertion, and the occasional presence of "fever." She had required only three additional transfusions. The "varicose ulcers" had healed. During the week immediately preceding her second hospitalization, she was completely free of any diarrhea, although her stools were black on several occasions. She denied any history of jaundice, intake of hepatotoxic drugs or exposure to toxic chemicals.

On physical examination the blood pressure was 112/80 mm. Hg, pulse 80, respirations 16 and temperature 37.6°C. The patient was cachectic, ascitic, chronically ill, but in no acute distress, alert and cooperative. The physical examination differed from that described on the first admission as follows: wasting of cranial musculature; palpable shotty nodes in the neck; dullness, decreased fremitus, absent breath sounds and "crackling" rales over both lung fields up to the tip of the scapula; absence of visceromegaly in the abdomen; distention of the abdomen in a symmetric distribution with obvious ascites; engorged collateral veins (superficial hypoglossal, inferior and superior epigastrics and external mammary with predominant flow in a superior direction); sacral edema up to the height of the scapula; and 2-plus pitting edema of the lower extremities.

Laboratory data were as follows: The white blood cell count was 5,900 per cu. mm. with 57 per cent segmented forms, 9 per cent bands, 3 per cent eosinophils, 30 per cent lymphocytes and 1 per cent monocytes. The hemoglobin was 8.6 gm. per cent, reticulocyte count 1.8 per cent; the platelets appeared to be adequate, but the red blood cell morphology was described as hypochromic with slight anisocytosis. The urine specific gravity was 1.013, pH 4.5, protein trace, with a negative sugar reaction, 10 to 12 white blood cells and 6 to 8 red blood cells were seen per high power field in centrifuged sediment. The stool examination on admission had a positive guaiac reaction, 2-plus benzidine reaction. During the remainder of hospitalization there were eight other examinations of the stool for blood, all were negative. The fasting blood sugar was 89 mg. per cent, blood urea nitrogen 16 mg. per cent, calcium 10.1 mg. per cent, phosphorus 3.5 mg. per cent, alkaline phosphatase 2.8 Bodansky units. Albumin was 2.7 gm. per cent, globulin 3.7 mg. per cent, cephalin cholesterol flocculation 3 plus, thymol turbidity 6.2 and bilirubin less than 0.8 mg. per cent. Serum glutamic oxaloacetic transaminase was 36 units, serum glutamic pyruvic transaminase 10 units, and prothrombin time 70 per cent of the normal value. Serum sodium was 136 mEq. per L., potassium 4.1 mEq. per L., carbon dioxide 26.2 mEq. per L. and chloride 99 mEq. per L. Roentgenographic examinations of the chest, upper and lower gastrointestinal series and oral cholecystograms, revealed discoid atelectasis of both lower lobes; bilateral pleural effusions or thickening; minimal left ventricular enlargement; minimal scoliosis of the dorsal spine; pulmonary fibrosis, upper lobe of right lung; increased intraperitoneal fluid; gallstones; probable esophageal varices; (?) pulmonary infarct; compression fracture of the third lumbar vertebra with degenerative osteoarthritis; Cushing clips.

On the third hospital day, the red blood cell count was 2.97 million per cu. mm., hemoglobin 8.1 gm. per cent, reticulocyte count 4.6 per cent. The red cell constants were mean corpuscular volume $81 \mu^3$, mean corpuscular hemoglobin 27 $\mu\text{g}.$, and mean corpuscular hemoglobin concentration 34 per cent. See Table I for further hematologic findings. Aspirated sternal bone marrow was cellular, containing normal myeloid and megakaryocytic elements, with slight stimulation of the erythroid elements. On the eleventh

TABLE I
SUMMARY OF HEMOGRAMS

	9/22	9/24	9/30	10/10	4/19	4/22	5/8	5/13	5/15	5/20	5/27	6/1
Red blood cell count (per cu. mm.)	3.82	4.41	4.93	2.91	1.75	1.49	1.91	2.52	2.65
Hemoglobin (gm. per cent)	13.7	13.8	12.1	8.6	8.1	4.3	5.0	5.9	6.4	8.5	8.9
Reticulocytes (%)	2.0	3.0	1.8	4.6	40.0	47.0	42.4	18.2	2.5	6.2
Platelets	220,000	295,000	196,000	94,000	49,000	20,000	61,000	300,000	212,000
White blood cell count (per cu. mm.)	4,850	4,550	7,150	5,950	5,900	7,750	18,300	18,200	10,200	7,150	5,200	9,250
Segmented forms (%)	59	53	64	54	57	55	57	56	54	69	63	81
Bands (%)	6	6	5	9	5	11	23	13	7	4	2
Metamyelocytes (%)	1	1	6	9
Myelocytes (%)	3	3	4
Eosinophils (%)	2	1	7	3	9	1	2
Basophils (%)	2	2
Lymphocytes (%)	35	34	28	25	30	21	27	9	13	15	27	12
Monocytes (%)	6	5	1	7	1	9	1	5	5	9	5	5

hospital day, a pelvic venogram demonstrated complete occlusion of the right common iliac and femoral veins. An attempt to localize the obstruction by inserting a catheter into the inferior vena cava was unsuccessful because of thromboses in the arm veins; insertion of the catheter into a jugular vein was not attempted. The patient was seen in consultation regarding the feasibility of a portal caval shunt. On May 5, 1959, 2 L. of grossly bloody fluid was removed from the abdominal cavity; specific gravity was 1.015, total proteins 3.7 gm. per cent (albumin 1.8 gm. per cent, globulin, 1.9 gm. per cent), cell block was negative. Culture of the fluid resulted in the growth of *Bacillus subtilis* in the thio broth alone. The paracentesis wound leaked minimal amounts of serosanguineous fluid. Exploratory laparotomy was scheduled but subsequently cancelled because of inability to cross-match any blood for the performance of surgery. A high titer positive Coombs' test was obtained and the hemogram on this day was markedly altered. The white blood cell count was 18,300 per cu. mm., hemoglobin 4 gm. per cent, hematocrit 13 per cent, reticulocyte count 40 per cent, platelet count 94,000 per cu. mm. The patient had become quite dyspneic on the least exertion and was slowly reaccumulating ascitic fluid. Serum bilirubin was 3.1 mg. (total), 0.5 mg. per cent (direct), and 2.6 mg. per cent (indirect). Patient's own serum was noted to agglutinate her own red blood cells *in vitro* at room temperature with bovine albumin, and all attempts at cross-matching blood resulted in agglutination. The patient was treated with Decadron® 0.75 mg. every six hours; she felt better within forty-eight hours, but there was no objective hematologic improvement. After receiving Decadron, 1.5 mg. every six hours for

one week, the reticulocyte count was 47 per cent and hemoglobin 5 gm. per cent. Electrophoretic analysis of her serum showed increased gamma globulin and decreased alpha₂ globulin and albumin. After two weeks of steroid therapy there was definite hematologic and clinical improvement; at three weeks the reticulocyte count was 2.5 per cent and the hemoglobin 8.5 gm. per cent. The platelet count was 212,000 per cu. mm. By June 4 the patient had improved enough to permit an exploratory laparotomy. She died on the fourth postoperative day.

CLINICAL DISCUSSION

DR. CARL V. MOORE: This patient presented a confusing diagnostic problem to the physicians who were caring for her. In 1929, during the first pregnancy at the age of twenty-eight, edema of the ankles developed and persisted until she died thirty years later. About 1938, varicose ulcers appeared on her ankles. In 1949, at the time of venous ligations, she was told that she had abdominal varices. In February 1957 and in January 1958, there were two episodes said to be pneumonia; but it is immediately obvious that these may have been caused by pulmonary infarcts. She had an anemia requiring twenty-nine transfusions which was first recognized in February 1947; it was said to have disappeared or to have corrected itself by approximately May 1958. Subsequently additional transfusions were necessary. In September 1957 she complained of abdominal distress. Several months later, abdominal swelling occurred and was present intermittently from then on. She had dyspnea and chest pain from about March to September 1958.

When she was admitted to the hospital for the

first time on September 22, 1958, she had edema and ulcers of the ankles, evidences of collateral circulation over her abdomen and thorax, several 3 by 4 cm. lymph nodes in both axillae, the first mitral and second pulmonic heart sounds were accentuated, and there was a moderately loud systolic murmur at the apex. Her liver was moderately tender and palpable 3 cm. below the costal margin. The blood count was essentially normal; urine showed 1-plus proteinuria; there were laboratory evidences of parenchymal hepatic damage; a biopsy specimen of the liver showed changes of hemosiderosis; splenomegaly and a compression fracture of the third lumbar vertebra were detected on the roentgenograms. She was treated conservatively, seemed to respond, and was discharged about the middle of October. She remained fairly well until January 1959, when intermittent vomiting and diarrhea developed, and there was a loss in tissue weight, and an increase in the edema. Shortly before her second admission she had melena.

Her second and final admission was from April 18 to June 9, 1959. Results of her physical examination varied from that on the first admission in that there was wasting, small shotty lymph nodes in the neck, evidence of partial consolidation of both lower lungs, ascites and the edema extended to the sacrum. She had 8 gm. of hemoglobin and again 1-plus proteinuria. The blood urea nitrogen was normal as were most of the other blood chemical determinations. Results of the hepatic function tests remained abnormal. Ascitic fluid was found to be bloody; the cell block was negative. The patient then had an interesting dramatic episode of acute hemolysis associated with autoagglutination of her red cells, a positive Coomb's test and thrombocytopenia. She was treated with steroids and there was a moderate response. An attempt at right heart catheterization had to be abandoned because all veins exposed were found to be thrombosed. She recovered enough to permit surgical exploration of the abdomen early in June. That is the end of the report.

The diagnostic problem involves a patient who was found to have thrombosis of both common iliac veins, and probably of the inferior vena cava, involvement of the liver, the red blood cells, the platelets and possibly the lymph nodes. Is this all one disease, or did she have an old process which was responsible for the edema of

the ankles and thrombosis of the inferior vena cava, with a new lesion superimposed? We obviously need all the help we can get, Dr. Humphrey have you been able to piece together from the roentgenological studies more than the protocol indicates?

DR. HARVEY A. HUMPHREY: The chest roentgenogram taken on admission in September 1958 showed an elevated diaphragm, considerable infiltration and fibrosis, and discoid zones of atelectasis bilaterally. There were some nodular densities elsewhere in the lungs that probably represented thrombosed veins without infarction, although there were also areas which represented organizing multiple pulmonary infarcts. Seven months later a large density had appeared in the left lung with no change in the right lung. A gastrointestinal examination was performed in September 1958. There probably were some small varices in the region of the cardia. The duodenal loop appeared normal. There was no evidence of a pancreatic tumor. A compression fracture of the third lumbar vertebra with depression of the superior cortex was seen. This appeared to be a post-traumatic fracture. Films taken in 1959 showed esophageal and periesophageal varices. A transitory pressure defect was seen on the second and third portion of the duodenum. In view of the presence of ascites, this probably represented fluid in the retroperitoneal sac. At no time was any mucosal abnormality seen in the duodenum, merely eccentric pressure. A few gallstones were seen in the gallbladder, although the gallbladder was not distended. A venogram using the right common femoral vein was performed. Collateral vessels were demonstrated in the anterior abdominal wall as well as retroperitoneally varices. Neither the iliac vein nor the inferior vena cava were opacified, so we concluded that they were occluded. The anterior and posterior abdominal wall vessels terminated in the internal mammary vessels and in the diaphragm. These collaterals appeared to be circumventing the inferior vena cava. We did know that the patient had evidence of splenomegaly, esophageal varices and gastric varices. This knowledge, plus the fact that we could not enter an arm vein, suggested that she had multiple deep venous occlusions. The liver was never obviously abnormal in size. An intravenous pyelogram was performed after the venogram. This film was taken about four minutes after injection. Both kidneys could be seen. No dye

was seen in the ureters, which is a little unusual five minutes after a dye examination, but not obviously abnormal. The only reason I pause, is that there is an entity that has been written about recently; namely, retroperitoneal fibrosis or periureteral fibrosis. At times this results in occlusion of the inferior vena cava, but hydronephrosis due to bilateral ureteral obstruction is a much more common feature. In summary, all we have is evidence of multiple deep major vein thrombosis.

DR. MOORE: It would be profitable to decide how extensive the thrombotic disease was in this patient. We have evidence to indicate that there was obstruction of the common iliac veins and probably of the inferior vena cava. The process involved the veins in her arms. In all probability, she had pulmonary infarcts. Dr. Bricker, did the obstruction of the inferior vena cava extend high enough to involve the renal veins? She had 1-plus proteinuria. A cholesterol determination on the first admission was 134 mg. per cent.

DR. NEAL BRICKER: If the renal veins are totally obstructed, the kidneys may become infarcted. However, if some lumen persists, one generally finds a fairly well characterized sequence of events beginning with proteinuria, often of great magnitude, and frequently followed by the sequential changes of the nephrotic syndrome. There may be some degree of azotemia, and microscopic hematuria is frequently observed. The kidneys are often enlarged and may be unequal in size. This patient had minimal amounts of protein in her urine, as judged by the qualitative tests, and manifested none of the abnormalities of the nephrotic syndrome. Moreover, her blood urea nitrogen was never markedly elevated. I think it is conceivable that the inferior vena cava was thrombosed up to the level of the renal veins, but I would be surprised if the venous return from both renal veins was significantly compromised.

DR. MOORE: It is true is it not, that if the thrombosis or the occlusion is slow, there may be time for collateral circulation to develop? Under these circumstances involvement of the inferior vena cava may occur about the level of the renal veins with just moderate proteinuria and little functional disturbance.

DR. BRICKER: Yes.

DR. MOORE: We could at least record a question mark about involvement of the renal veins. If they were thrombosed, collateral cir-

culation would have developed, or the nephrotic syndrome would have appeared. Dr. Shank, the house officers were trying to determine whether or not involvement of the portal vein was also present. That was the reason for performing a glucose tolerance curve with blood obtained both from a peripheral vein and from the collateral veins on the abdomen. Would you interpret the two curves for us?

DR. ROBERT E. SHANK: It is difficult for me to draw any conclusions from the information. There was relatively little difference between peripheral and collateral concentrations of glucose. It has been pointed out that there was evidence of obstruction of both common iliac vessels. In view of this finding, interpretation of the blood glucose levels is difficult.

DR. MOORE: If the collateral veins on her abdomen had been coming largely from the portal circulation, the glucose level would have been considerably higher than in the peripheral circulation. Since that differential was not observed, the test was of little help. Dr. Karl, what was happening to this patient's liver? A diagnosis of hemosiderosis had been made on the basis of a biopsy; hepatic function tests were abnormal and esophageal varices and a large spleen were present.

DR. MICHAEL M. KARL: One would like to put this all together by saying that this patient had cirrhosis with portal hypertension leading to the establishment of the esophageal varices. Along these lines, it would be nice to be able to say that this patient also had portal thrombosis, in view of the fact that she had evidence of venous occlusion elsewhere. However, you have already pointed out that in the differential glucose tolerance curve, these curves do not suggest that portal thrombosis plays a major part. Also the description and the direction of the blood flow of the collateral veins described are not consistent with the findings in portal thrombosis alone. These veins are described as showing blood flow upward throughout most of the abdomen. These findings are certainly much more consistent with thrombosis of the vena cava than with thrombosis of the portal vein, in which the blood flow usually flows away from the umbilicus.

DR. MOORE: Yes, but if we assume that the collateral veins on the abdomen were really due to the obstruction of the inferior vena cava, is it not possible to make a pretty good case for portal vein thrombosis anyway?

DR. KARL: If we make a case for portal vein thrombosis alone, we would have difficulty in reconciling the glucose tolerance curves, because in the presence of portal thrombosis, the collateral veins show glucose concentrations similar to those found in the portal blood.

DR. MOORE: But when the collateral veins are carrying blood both from the portal circulation and from the systemic circulation, might you not erase these differences?

DR. KARL: Yes, but this would imply a considerable amount of compensating collateral blood flow. I think we can say, regardless of whether portal thrombosis is present, that this patient had some diffuse hepatocellular disease as evidenced by the fact that the cephalin-cholesterol flocculation test was positive and that the globulin and blood transaminases were elevated. I cannot say whether portal thrombosis complicated this diffuse hepatocellular disease. I am inclined to believe that the evidence is against this, since the roentgenogram did not show any conclusive evidence of esophageal varices.

DR. MOORE: Could this degree of hepatocellular damage be present if there were involvement of some of the hepatic vein radicles?

DR. KARL: If hepatic vein thrombosis were present the liver would be enormously enlarged and there would be more striking evidence of diffuse hepatocellular disease than was seen here.

DR. MOORE: I do not mean the major hepatic vein, but radicles of the hepatic vein.

DR. KARL: Even with thrombosis of the smaller hepatic vein radicles, if enough of them are involved, there is usually evidence of severe, hepatocellular damage, with profound changes in laboratory test results. Usually these patients show a considerably greater degree of jaundice than was present in this patient, and with it a much more severe degree of hepatic failure.

DR. MOORE: What kind of hepatic disease do you think she had?

DR. KARL: I think that she probably had early mild cirrhosis, nutritional in origin possibly, rather than liver disease on the basis of hepatic vein thrombosis.

DR. MOORE: It is also possible that she might have had infarcts of mesenteric veins which would account for some of her gastrointestinal symptoms. Dr. Goldman, what are some of the causes of thrombosis of the inferior vena cava?

DR. MELVIN GOLDMAN: For clarity, let us say a word about varicose veins. When we say varicose veins, we mean dilated veins. Any vein can become a varicose vein if it becomes dilated, except for those veins in an A-V fistula or in an angioma. Now in general, there are two types of varicose veins: a primary type and a secondary type. In the primary type there is a hereditary weakness in the valves. As we grow older these valves become obliterated, and with an increase in pressure the veins become dilated. The secondary type develops following venous obstruction. In our patient, who had varicose veins and venous obstruction, the role of multiple pregnancies should be considered as a possible factor in the etiology of inferior vena caval occlusion. There are three mechanisms in pregnancy whereby the inferior vena cava may be obstructed. First, the mechanical pressure on the iliacs by the fetus. Second, an increase in intra-abdominal pressure, and third there is an increase in blood flow and blood volume from the internal iliac veins going into the common iliac veins. This interferes with the blood flow from the external iliac veins.

DR. MOORE: I guess that phlebothrombosis or thrombophlebitis is the most common cause of inferior vena caval thrombosis, is it not?

DR. GOLDMAN: That is correct.

DR. MOORE: What else may cause thrombosis?

DR. GOLDMAN: Intra-abdominal tumors or malignancies, aneurysms, ascites and adhesive bands following other types of surgery may cause thrombosis.

DR. MOORE: I suppose retroperitoneal or periureteral fibrosis could be added, but in this instance the history would seem to indicate that phlebothrombosis was primarily responsible. The pulmonary infarcts could have come from thrombi in the legs, but we still must worry about why the thromboses developed in her arm veins, and possibly in the portal and hepatic veins as well. The house staff was disturbed about this patient because her blood clotted in syringes despite all precautions. Dr. Fletcher, is there such a thing as hypercoagulability, and if so, what causes it?

DR. ANTHONY FLETCHER: I suppose the term "hypercoaguable state" is used with two meanings: first of all the diagnosis is suggested when a thrombosis develops for which there is no apparent cause, and second, the term is sometimes used to describe abnormal reactions to laboratory tests for various types of coagulant

factors. Unfortunately, the correlation between the laboratory tests and cases of multiple thrombosis tends to be poor. There are certain situations, for instance, in patients suffering from abruptio placenta in which it is possible to demonstrate the presence of thromboplastic material in the blood; this finding correlates well with the clinical state. There is also a suggestive correlation between the stopping of long term anticoagulant therapy, the rise in the various coagulation constituents, and subsequent thrombosis. But hypercoagulability is a vague concept; three reasons may be suggested to explain this failure of correlation between the clinical state and laboratory tests: (1) The clinical state and the examination of the blood were in no way related. One reason for this might be that the clinical state is due to a disease of the vessels or a slowing of the blood flow or some other factor. (2) The coagulation tests employed for the purpose of demonstrating a hypercoagulable state are inappropriate for the purpose, and in this regard I would like to mention a recent paper of Spaet's* in which he points out the crude nature of the tests that are usually used in the laboratory to determine the over-all coagulability of the blood. He points out that there are no *in vitro* tests that give a corresponding type of determination to that suggested by Wessler,† in which blood coagulation is assessed following double ligation of a vein in an animal. Spaet himself suggests a simplified test in which the coagulation of the blood is determined in plastic tubes. Using this "technic," which appears to offer significant advantages over those in present use, Spaet found that the feeding of butter fat did not produce a hypercoagulable state, whereas others who have used standard *in vitro* tests describe the production of hypercoagulability after feeding butter fat. The third possibility is to us an intriguing one, involving the hypothesis that the "hypercoagulable" state may exist independently of abnormal coagulation phenomena, its manifestations being caused by failure of the plasminogen-plasmin system to lyse microthrombi. For lack of proper technical method, this possibility has never been adequately

investigated, but we do have preliminary data indicating that such a theory might be relevant to the problem.

DR. MOORE: The fact that thrombocytosis and tumors of the body or tail of the pancreas, the bronchus and the stomach, may cause multiple venous thromboses, is so well known that it needs no further comment. The clinical and diagnostic data make any of these possibilities seem unlikely. Dr. Goldman, do you think this could be thromboangiitis obliterans with involvement of the veins for all these years without overt arterial lesions?

DR. GOLDMAN: I would not consider that possibility very seriously here.

DR. MOORE: Dr. Vavra, can you make any other suggestions?

DR. JOHN VAVRA: A rather interesting group of patients was described in 1949 by Gerber and Mendelowitz in the *Annals of Internal Medicine*. The clinical course in their patients was very similar to the one in this patient. All patients had multiple, severe and devastating thromboses, without demonstrable underlying disease, which involved, at one time or other, almost every vein in the body. The thromboses occurred both in superficial veins and in deep veins, but those in the deep veins predominated and presented the major problems to the patients. The patients reported with this illness, which is called visceral thrombophlebitis migrans, were under fifty years of age. Six patients reported on by these two authors were below the age of forty-five when their illness began; this was also true for our patient if you can date the onset of illness back to 1928. The symptoms and signs depended upon the veins that were thrombosed, and since all deep visceral veins were subject to thrombosis a wide variety of symptoms were encountered. Almost all the patients had multiple and recurrent pulmonary infarcts. The patients often had thromboses of the inferior vena cava, of small areas of the portal and hepatic veins, adrenal veins and renal veins, making it surprising that they were able to survive for an average of three or four years. The reason appears to be that only small areas of veins were involved at any one time and these veins later recanalized. In most of the patients ascites developed at one time or another, often bloody, and presumably due to thrombosis of mesenteric and portal branches. Although the authors claimed that the results of liver function studies were normal, the case histories of

* SPAET, T. H., CINTRON, J. and KROPATKIN, M. A technique for determining whole blood clotting times in plastic tubes. *J. Lab. & Clin. Med.*, 54: 467, 1959.

† WESSLER, S. Studies in intravascular coagulation. I. Coagulation changes in isolated venous segments. *J. Clin. Invest.*, 31: 1011, 1952.

several of these patients showed abnormalities in these tests, presumably due to thrombosis of hepatic radicles. Some patients had fairly long remissions, probably due to recanalization of the vessels, but the thromboses eventually reappeared and led to the death of the patient. Fever and leukocytosis was a feature when severe thrombosis had occurred. In some patients the platelet count was decreased. The authors suggested that this was due to sequestering of platelets in the area of thrombosis. In none of the patients was a hemolytic anemia described. It would appear that our patient would fit into this group described by Gerber and Mendelowitz. I think the terminal episode was another severe thrombosis occurring in the abdomen.

DR. MOORE: Dr. Chaplin, would you tell us what you think happened to the erythropoietic system in this patient? Did she have "autoimmune hemolytic anemia" since 1957 or did she then have another kind of anemia, one secondary to dysplasmia caused by splenic vein thrombosis?

DR. HUGH CHAPLIN: The latter possibility cannot be excluded, but it seems unlikely to me that such a condition would cause such profound anemia as to require twenty-nine transfusions over that interval of time. Of course, if she were bleeding at the time from varices, this could have contributed to the high transfusion requirement, but again I think hemorrhage is unlikely. The presence of hemosiderin in the liver biopsy specimen is strongly in favor of retention of the products of red cell destruction rather than loss of blood through the gastrointestinal tract. I am impressed that this woman had two problems: one, hemolysis, and another, inadequate marrow response. She had so many clinical difficulties that an acquired hemolytic anemia might well have occurred in relation to any of them. I am a little bit inclined to attribute her earlier respiratory symptoms to pneumonia rather than infarcts, because of the chills and fever that accompanied them. It is attractive to me that she may have had a virus pneumonia in 1957 with the development of the rather severe hemolytic anemia that sometimes accompanies this illness and usually is associated with cold agglutinins and cold incomplete antibodies of an autoimmune type. Unfortunately, we do not have the necessary hematologic data to confirm this. It is characteristic of this syndrome on occasion to wax and wane and sometimes to

persist over a period of as long as seven or eight years. I am tempted again to guess that in 1957 she had an episode of hemolysis which gradually remitted, but recurred late in her illness, perhaps in response to infection in the genitourinary tract, perhaps to reinfection in the pulmonary system. We did not have an opportunity to make antiglobulin studies in our own laboratory during her final admission, therefore the characteristics of her autoantibody are unknown, but the marked autoagglutination that created such a problem in the blood bank frequently accompanies the "non-gamma globulin" type of cold autoantibody which could well have originated during her respiratory infection in 1957.

DR. MOORE: Even though it is recognized that this patient might possibly have had a secondary disease, such as lymphoma, carcinoma of the pancreas or cirrhosis of the liver, I am inclined to agree with Dr. Vavra that the whole disease was essentially one process from beginning to end: visceral thrombophlebitis migrans. Now Dr. Butcher, would you tell us what you found at the exploratory laparotomy?

DR. HARVEY BUTCHER: This patient had much ascites, which was no longer grossly bloody at the time of abdominal exploration. The spleen was two and a half times normal size, and its outer surface was covered with irregular yellow slightly depressed or elevated areas, which were firm. Near the anterior border of the left hepatic lobe was a discrete nodule which was irregular, firm and paler than the surrounding liver. The rest of the liver was nearly normal in appearance. The retroperitoneal tissues were edematous and indurated; edema involved the root of the small bowel mesentery. The following procedures were performed: the liver nodule was biopsied; a frozen section showed the nodule to be a hamartoma. The root of the small bowel mesentery where the greatest induration seemed to be, was mobilized, and a large retroperitoneal lymph node which was removed showed only hyperplasia. The inferior vena cava was then exposed in the center of the retroperitoneal induration. The vena cava was so firm that a biopsy specimen of the wall was secured. The vena cava was thickened but had channels in it which bled briskly. Finally the spleen was removed because of the hemolytic anemia. The procedure was carried out rather rapidly because of the poor condition of the patient. Portal pressures for example, were not taken. Her blood pressure was 60-70/40-50 mm.

Hg after fifteen minutes of operating; at hypotensive levels, portal pressures mean very little.

DR. MOORE: Dr. Rosenberg will tell us what the surgical pathologists found, and then Dr. Williamson will present the gross autopsy findings.

DR. BARBARA ROSENBERG: The first two biopsies have already been mentioned. The axillary lymph node was normal and the needle biopsy specimen of the liver showed hemosiderosis. There was also an ascitic fluid specimen which was negative for tumor cells. The spleen which Dr. Butcher removed showed several depressed areas and on cut surface there were numerous yellow nodules beneath the capsule which microscopically proved to be old infarcts. There was also a massive amount of hemosiderin. A lymph node from the splenic region also showed marked hemosiderosis. The lesion Dr. Butcher described in the liver proved to be a hamartoma which appeared to be composed chiefly of sclerotic vessels. In one area of the liver biopsy specimen there were several vessels which appeared very thick walled; the marked changes in the walls made it difficult to decide in every case whether these vessels actually represented arteries or veins. An elastic tissue stain showed a discontinuous elastic membrane in some of these vessels. In some there was almost complete obliteration of the lumen; whether this was entirely the result of endothelial proliferation or of organized thrombi is impossible to say. No recent thrombi were seen in these sections, and there was no evidence of a significant degree of arteritis. These vascular changes were not sufficient to give us a definitive diagnosis; the possibility of an arteritis of some sort was entertained, but we did not believe that we had adequate material to make this diagnosis.

PATHOLOGIC DISCUSSION

DR. JOSEPH WILLIAMSON: The appearance of the body at autopsy was that of a well developed, but poorly nourished cachectic white woman who appeared much older than her stated age. The upper extremities were markedly wasted; the lower extremities were edematous, the level of edema extending up to the umbilicus. The skin of the ankles and legs was darkly pigmented, indurated and scaly, and these changes were more marked on the left side than on the right. The abdomen was distended and the superficial veins were quite dilated. An unhealed

recent surgical incision was present in the mid-epigastrium. Several small petechiae were present on the skin of the face and over the thorax. The abdomen contained 7,500 cc. of a sanguineous fluid which had a hematocrit of 12 per cent. Both leaves of the diaphragm were markedly elevated to the second and third intercostal spaces on the right and left sides, respectively. In the left upper quadrant several foci of fat necrosis and a recent thrombus in the splenic vein at the site of surgery were seen. Two hundred cubic centimeters of fluid similar to that seen in the abdomen was present in each pleural space, and dense fibrous pleural adhesions were present bilaterally. The lungs were moderately congested and atelectatic, and a large thrombus was present in the left pulmonary artery. This completely filled the pulmonary artery, was slightly adherent, and partially organized. The gross appearance of the heart was within normal limits, and arteriosclerosis in the coronary arteries and aorta was minimal. In the superior vena cava there was a partially organized mural thrombus about 2 cm. in diameter. This was approximately 8.5 cm. proximal to the tricuspid valve, and was attached to the wall of the superior vena cava by a narrow pedicle. It was freely mobile. Additional thrombi included one completely organized mural thrombus in a radicle of the portal vein and an old organized recanalized thrombus in the splenic vein. The lumen of the lower two-thirds of the inferior vena cava was completely obliterated by dense fibrous tissue. This extended from a level just below the openings of the hepatic veins, and extended caudally involving both renal veins and both common iliac veins. The vena cava and both renal veins were reduced to fibrous cords in which small recanalized vessels were discernible on the cut surfaces.

At autopsy, the only demonstrable collateral venous circulation from the kidneys consisted of enlarged veins in the proximal ureter and hilus, which were quite dilated, especially on the left side. The renal capsular vessels were neither enlarged nor dilated. Unfortunately the extent of thrombosis of the vena cava was not appreciated until after the relationships of some of these collateral veins had been disturbed. In addition to the dilated superficial vessels of the abdomen, the longitudinal vertebral sinuses and the internal mammary veins were quite dilated. The kidneys were of normal size, the right

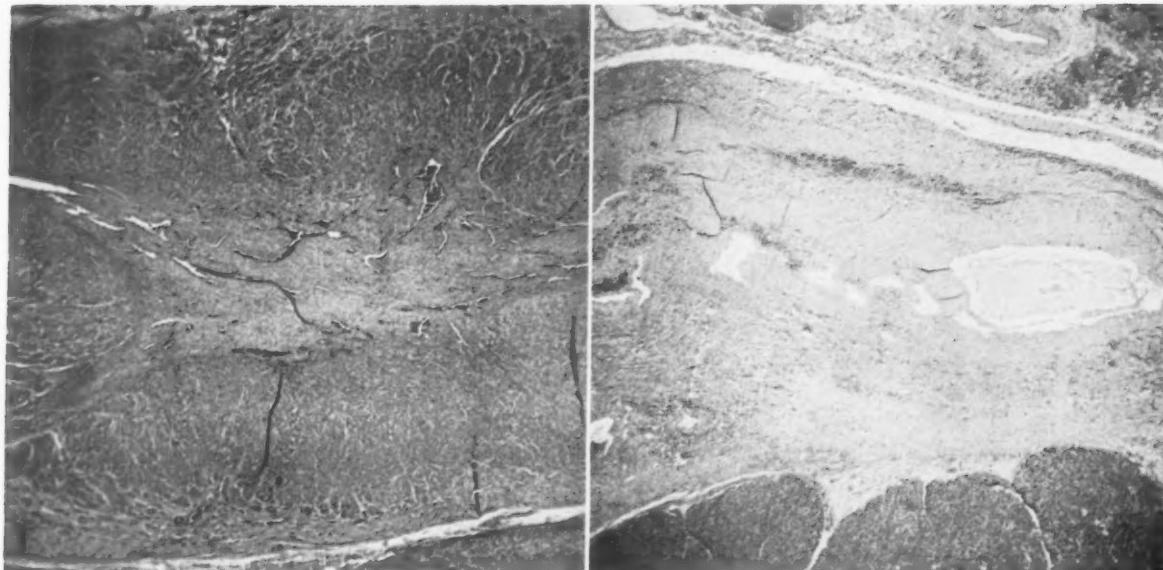


FIG. 1. Inferior vena cava at level of the liver with remote occlusion and recanalization. Hematoxylin and eosin, original magnification $\times 150$.

FIG. 2. Splenic vein with remote occlusion and recanalization. Hemosiderin is still present within the organized thrombus. Hematoxylin and eosin, original magnification $\times 150$.

weighed 160 gm. and the left, 130 gm. The capsule stripped with ease and revealed finely granular surfaces with several irregular depressions in the cortex. The liver appeared normal except for a moderate centrilobular congestion and some necrosis at the site of biopsy. Several small black pigment stones were present in the gallbladder, and one such stone approximately 3 mm. in diameter was present in the common duct, about 2.5 cm. proximal to the ampulla. The terminal 70 cm. of the large colon was markedly congested and edematous, and several extensive areas of necrosis and ulceration were present in the mucosa. The mucosa of the entire gastrointestinal tract was slightly edematous. No esophageal or gastric varices were seen at autopsy.

DR. GEORGE SORENSEN: Histologic sections of the inferior vena cava from just below the entrance of the hepatic veins and at varying levels below this, appeared similar. (Fig. 1.) The lumen was filled with dense fibrous tissue within which there were a few small vascular channels which apparently represented a limited amount of recanalization. The microscopic appearances of the occluded iliac and renal veins were the same as the inferior vena cava. These occlusions were evidently of long duration although the exact age could not be determined. The splenic vein was also completely occluded with fibrous tissue within which there were

small vascular spaces and hemosiderin. (Fig. 2.) Some of the latter was within macrophages and some free within the tissue. This occlusion was probably of more recent origin, but still of moderately long duration. Evidence of increased collateral circulation was observed microscopically in the liver capsule and the renal pelvis. In both sites there were many dilated vascular spaces.

The base of the mural thrombus within the superior vena cava was well organized, but the superficial portion was of recent origin. The left main pulmonary artery was completely occluded. This lesion was of relatively short duration, although organization was occurring at the periphery. (Fig. 3.) In a few of the smaller pulmonary arteries there were partial to complete fibrous occlusions and there were two small recent pulmonary infarcts. The portal vein contained a small organized mural thrombus which did not significantly limit the lumen. One of the larger hepatic arterial branches showed moderate intimal fibrosis, and within a few of the smaller branches of the hepatic artery there were fibrous occlusions with recanalization. (Fig. 4.) Microscopically, the liver contained much hemosiderin with Kupffer cells and parenchymal cells. This was confirmed by a Prussian blue stain of the liver section. There was also slight pericentral lobular atrophy in the liver. The kidneys contained evidence of slight

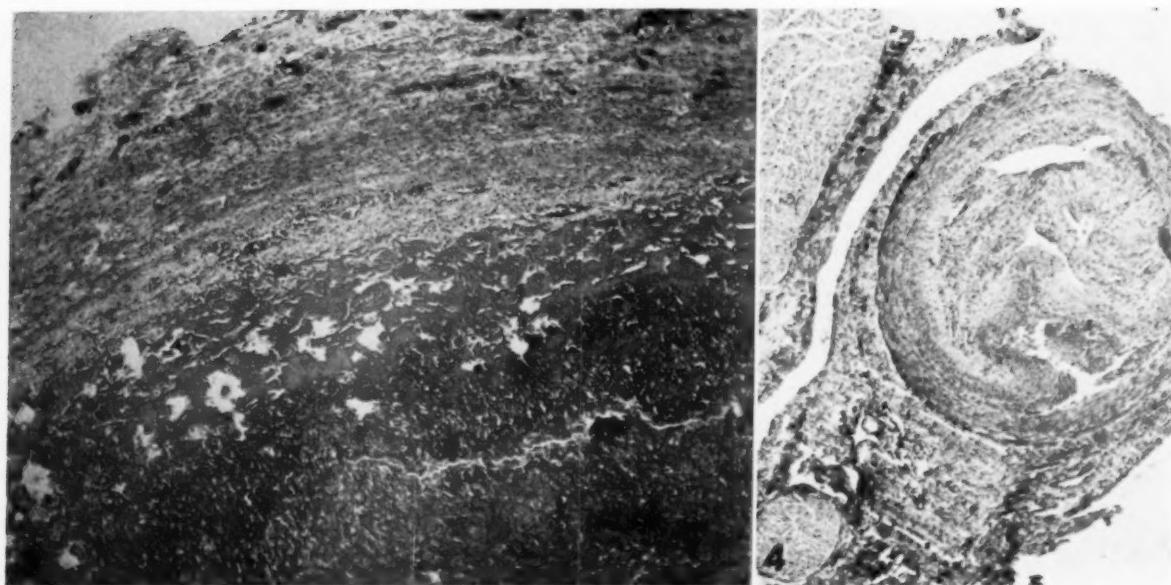


FIG. 3. Left main pulmonary artery with recent organizing thromboembolic occlusion. Hematoxylin and eosin, original magnification $\times 300$.

FIG. 4. A branch of the hepatic artery with remote occlusion and recanalization. Hematoxylin and eosin, original magnification $\times 450$.



FIG. 5. A portion of the colon showing acute pseudomembranous colitis. Hematoxylin and eosin, original magnification $\times 400$.

focal chronic pyelonephritis. The bone marrow showed erythroid hyperplasia.

Histologic sections of the colon demonstrated intense acute mucosal and submucosal inflammation with recent thrombotic occlusion of the submucosal vessels and necrosis of the epithelium. (Fig. 5.) These features were characteristic of pseudomembranous colitis.

The pathogenesis of this patient's disease is difficult to reconstruct. It is probable that the original thrombophlebitis was in the lower extremities and the disease ascended to involve the vena cava and some of its tributary veins. At the time of death only the scars of the disease remained and the effects of them, i.e., the fibrous occlusions of many contiguous veins. The partial to complete occlusions of some of the pulmonary arteries were probably caused by thromboemboli which had developed in the diseased veins at various times.

The largest series of cases of vena caval obstructions was reported in 1911.* Of this group, about 20 per cent were of unknown cause, although the vena caval thrombosis usually was thought to be secondary to venous thrombosis in the vessels draining into the vena cava. This case would fit into this category. The widespread involvement of the abdominal veins would also make this case similar to what has been described as visceral thrombophlebitis migrans.† However, the involvement of hepatic arteries would be atypical for the latter designation.

The primary anatomical diagnoses are as follows: fibrous occlusion of inferior vena cava

* PLEASANTS, J. H. Obstruction of the inferior vena cava with a report of 18 cases. *Bull. Johns Hopkins Hosp.*, 16: 363, 1911.

† GERBER, I. E. and MENDELOWITZ, M. Visceral thrombophlebitis migrans. *Ann. Int. Med.*, 30: 560, 1949.

(lower two-thirds), iliac veins and renal veins; dilatation of thoracoepigastric, lateral thoracic and internal mammary veins, marked, of longitudinal vertebral sinus and of small veins in the adventitia of the vena cava and portal vein, capsule of the liver and proximal ureters; marked edema of lower extremities up to umbilicus; ascites, 7,500 cc.; multiple old organized thrombi in the pulmonary arteries and recent partially organized thrombi in the superior vena

cava and the left pulmonary artery; recent small infarcts in the upper lobe of the right lung; organized thrombi in portal and splenic veins; fibrous occlusions with recanalization of branches of hepatic artery; hyperplasia of vertebral bone marrow; hemosiderosis of liver and bone marrow; chronic cholecystitis with cholelithiasis and choledocholithiasis; recent epigastric surgical excision; and pseudomembranous colitis, marked.

Case Reports

Acquired Hemolytic Anemia and Transient Erythroid Hypoplasia of Bone Marrow*

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THE occurrence of erythroid hypoplasia of bone marrow in acquired hemolytic anemia is sufficiently infrequent [1-3] to warrant a brief report of the following case.

L. F., a fifty-one year old white man employed as a shoe salesman, was admitted to South Nassau Communities Hospital because of weakness and pallor of three weeks' duration. The past history disclosed no serious illnesses. The patient had no complaints to report immediately prior to onset of the present symptoms. Occasionally he used various chemicals in dyeing shoes and had recently employed some chemical compounds in the garden, none differing from those he usually employed.

A prior admission to another hospital had disclosed a pale, well developed man, not appearing ill and free of complaints. Aside from pallor, the physical examination was within normal limits. No enlarged nodes, liver, spleen or masses were felt. Laboratory data revealed a hemoglobin of 5.7 gm. per cent, red blood cells 1.96 million per cu. mm., white blood cells 6,450 per cu. mm. with a normal differential count, platelets 150,000 per cu. mm., reticulocytes none, and occasional spherocytes. The blood group was AB, Rh positive, the results of the Coombs' test were positive, direct and indirect (against a panel of known cells). No cold or autoagglutinins were present; no L.E. cells were seen. There was no blood in the stools, or urine; the urine contained a trace of urobilinogen. The serum total bilirubin was 0.5 mg. per cent (direct 0.35, indirect 0.2). A hypotonic saline test of the patient's red cells showed beginning hemolysis at 0.44 per cent, complete hemolysis at 0.28 per cent (control 0.4 per cent and 0.32 per cent, respectively). Bone marrow aspiration revealed complete hypoplasia of erythroid elements.

Treatment with Medrol® was begun. All subsequent pertinent data are shown in Figure 1. After ten days of treatment the hemoglobin fell to 4.6 gm. per cent and the red cell count to 1.27 million per cu. mm. Reticulocytes were 0.5 per cent for the first time.

Results of the direct and indirect Coombs' tests remained positive.

At this time the patient was transferred to the South Nassau Communities Hospital for further studies. On December 21, 1957, the hemoglobin and red cell count were 3.8 gm. per cent and 1.40 million per cu. mm., reticulocytes 0.7 per cent, serum total protein 6.1 gm. per cent (albumin 4.3, globulin 1.8), direct Coombs' test positive, indirect test negative, spherocytes present. The serum total bilirubin was 0.55 mg. per cent (direct 0.26, indirect 0.29). No cold or autoagglutinins were present. The L.E. phenomenon was absent. A hypotonic saline test showed beginning hemolysis at 0.46 per cent, complete hemolysis at 0.36 per cent (control 0.44 and 0.32 per cent, respectively). No blood was present in the stools or urine.

The patient's blood was cross-matched with a donor of the same type and group. Results of the indirect Coombs' test were negative. The patient was given an intravenous injection of 25 ml. donor's blood, tagged with $\text{Na}_2\text{Cr}^{51}\text{O}_4$. Repeated surface body counting over the spleen, liver and heart did not show evidence of increased accumulation of radioactivity over any organ during a period of one hour. Samples of blood taken at five, ten, twenty, forty and sixty minutes showed no decline in activity in whole blood or increase in plasma activity. No hemoglobinemnia was present. Thereafter the remainder of this donor's blood (475 ml.) was administered slowly and without complication. Urine samples failed to show any hemoglobinuria. Subsequent daily transfusions of 500 ml. each were uneventful; a total of 4,500 ml. was administered. The serum bilirubin levels remained essentially the same. Bone marrow examination on the third day after this admission showed beginning erythroid regeneration (erythroblasts 2.8 per cent, normoblasts 4.4 per cent).

ACTH was included on the thirteenth day of Medrol therapy, as shown in Figure 1. The reticulocytes rose only moderately, the highest level being 4.9 per cent. On the eighth day after admission a bone marrow study revealed moderate erythroid hyper-

* From the South Nassau Communities Hospital, Oceanside, New York.

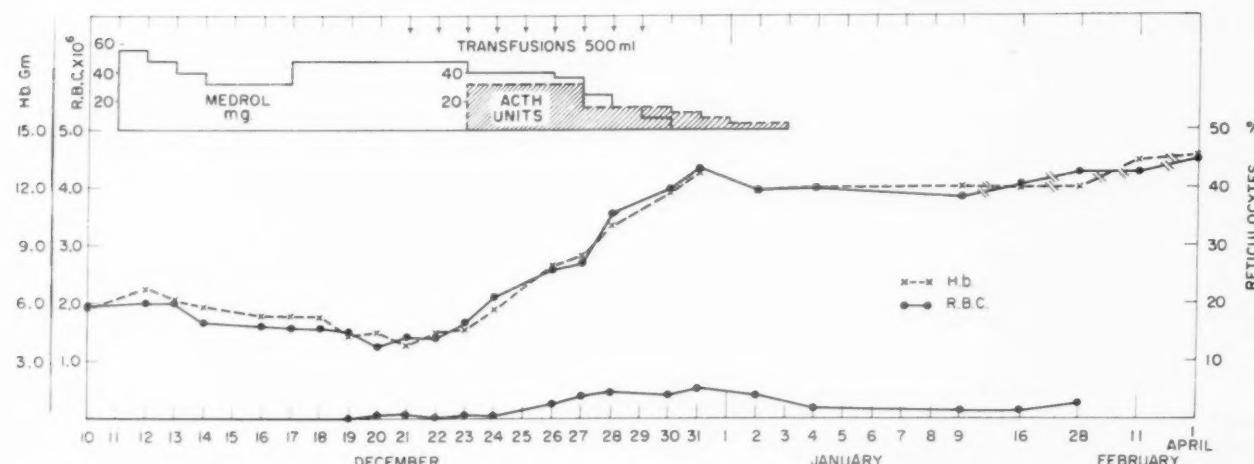


FIG. 1. Hematologic data and therapy in a patient with acquired hemolytic anemia and transient erythroid hypoplasia of bone marrow.

plasia (erythroblasts 8.5 per cent, normoblasts 32.7 per cent). The reaction to the direct Coombs' test remained positive, indirect was negative. Steroid therapy was gradually discontinued, as shown in Figure 1. When last seen four months after the onset of symptoms the hemoglobin and red blood cell count were at normal levels but the positive results of the direct Coombs' test persisted.

COMMENTS

Erythroid hypoplasia of bone marrow has been repeatedly observed in congenital hemolytic anemia, sickle cell anemia, in infancy and childhood, in association with thymic tumors, in normal children following infections or exposure to certain drugs, in paroxysmal nocturnal hemoglobinuria, and in a case of thalassemia minor [4-10]. Loeb et al. [11] described one patient with this bone marrow picture in whom evidence of an hemolytic process developed; there was a partial remission following splenectomy. However, the occurrence of erythroid hypoplasia of bone marrow with autoimmune hemolytic anemia has been reported only three times. In 1952 Davis and his associates [1] described a patient with a five-month history characteristic of severe hemolytic anemia, a negative reaction to the direct Coombs' test, moderate reticulocytosis and normoblastic bone marrow. As the patient's condition deteriorated, the reticulocytes disappeared, the results of the direct Coombs' test became positive and only occasional normoblasts were found in the bone marrow. Therapy consisted of repeated blood transfusions and the intramuscular administration of ACTH with satisfactory clinical and hematologic improvement. Subsequent splenec-

tomy (because of splenomegaly) was followed by complete remission, but the results of the direct Coombs' test remained positive. In 1953 Eisemann and Dameshek [2] described a patient with autoimmune hemolytic anemia, reticulocytes 0.3 per cent, and hypocellular erythroid bone marrow. The patient was treated with multiple blood transfusions, ACTH and cortisone. The reticulocytes disappeared, but the hypoplasia of red cell elements in bone marrow persisted. A splenectomy was performed. This resulted in a decreased need for blood transfusions. No reticulocytes were seen for seventeen days and the bone marrow remained hypoplastic. After this period reticulocytes began to appear and the bone marrow showed erythroid hyperplasia. Complete clinical and hematologic remission ensued, but results of the Coombs' test remained positive. In 1956 Bove [3] reported the third instance of erythroid hypoplasia of bone marrow and symptomatic hemolytic anemia which occurred in a patient with Hodgkin's disease. Autoagglutination of red cells was present. No reticulocytes were found in blood films and the bone marrow showed marked reduction of erythropoiesis. The patient was treated with cortisone. Six days later a reticulocyte appeared (0.1 per cent). Following this there was a satisfactory reticulocytosis, the bone marrow showed hypererythroblastosis, and clinical and hematologic remission followed. The results of the Coombs' test were negative.

The present case fulfills all the clinical and laboratory criteria for the diagnosis of acquired hemolytic anemia. In retrospect it appears that the appearance of 0.5 per cent reticulocytes on the tenth day of Medrol therapy heralded a

beginning remission. However, the patient's clinical condition was so poor that immediate transfusions were indicated. ACTH was added as Medrol was reduced since the reticulocytes remained at less than 1 per cent for four days and regeneration of erythroid elements in bone marrow was poor.

The role of steroids in the management of autoimmune hemolytic anemia is well established and requires no discussion in this report. There have been several reports suggesting that therapy with ACTH may be more efficacious than cortisone in acquired hemolytic anemia when the latter fails to evoke a satisfactory remission [12-15].

CONCLUSION

A patient with acquired hemolytic anemia with severe erythroid hypoplasia of bone marrow, successfully treated with steroids, is described. Clinical and hematologic remission persist even though results of the direct and indirect Coombs' tests remain positive.

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Elective Thymectomy in the Treatment of Aregenerative Anemia Associated with Monocytic Leukemia*

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RECENTLY there has been considerable interest in the association of tumors of the thymus gland with refractory anemia. A year ago we reviewed the literature and brought up to date two cases of our own which had been previously reported [27]. Both diseases are rare; their association, therefore, implies more than coincidence.

In Table 1 are presented all cases of benign thymoma associated with aplastic anemia

reported to date. There are seventeen of these cases. Chalmers [4] has stated that seven additional cases have been described to him by various doctors, both in England and this country. Case reports of variations of the syndrome, in which the tumor was not benign or in which there was depression of marrow elements other than red cells alone, have also appeared in the literature. Opsahl [16] reported a case of carcinoma of the thymus associated with anemia

TABLE I
CASES OF BENIGN THYMOA ASSOCIATED WITH HYPOPLASTIC ANEMIA

Author	Date Reported	Operation	Immediate Result	Late Result
Matras and Priesel.....	1928	None	Died
Davidsohn.....	1941	None	Died
Humphreys and Southworth.....	1945	Yes	Good response	Died
Chediak et al.....	1953	Yes	Good response
Chalmers and Boheimer.....	{ 1. 1954 2. 1954	Yes Yes	Improved, relapsed Unimproved	Improved on ACTH after splenectomy, died Improved on ACTH after splenectomy, relapsed
Bakker.....	1954	Yes	Good (died in 3 wk.)
Weinbaum and Thompson.....	1955	None	Died
Stibbe.....	1955	None	Died
Ramos.....	1956	Yes	Died
Bayrd and Bernatz.....	{ 1. 1957 2. 1957	Yes Yes	Unimproved Unimproved
Hartwell and Mermod.....	1957	None	Died
Mielke.....	1957	None	Died
Clarkson and Prokopp.....	1958	Yes	Unimproved
Ross, Soutter, Emerson, et al.....	{ 1. 1954 1958 2. 1954 1958	Yes Yes	Unimproved Unimproved	No response, died Complete remission

NOTE: Seventeen patients with thymoma associated with refractory anemia, as reported in the literature. Six came to autopsy without prior surgery, eleven underwent removal of the tumor.

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and leukopenia. Radojevic and Hahn [18] discussed a case in which pancytopenia was associated with a radiated mass in the thymic region. Polayes and Lederer [17] described a patient with mass in the anterior mediastinum and aplastic anemia. Josse and Zacks [13] reported a case of pancytopenia associated with benign thymoma and Wintrobe [24] has referred to the association of thymic hyperplasia and aplastic anemia. Recently, Clarkson and Prockop [7] reported a case (listed in Table 1) of thymic tumor associated with anemia; they also presented an interesting case history of a patient who had a huge thymoma removed in 1950, who returned two years later with an aregenerative anemia and a localized carcinoma of the breast [7]. A parallel might be drawn between this case and those in which patients have had thymic tumors removed only to have myasthenia develop subsequently. A number of such cases have been reported [9,10,21].

If there is a cause and effect relationship between thymic tumor and anemia, what is the effect of removing the growth? Because of the rarity of spontaneous remission in cases of aplastic anemia a favorable response would immediately assume some significance. Of the case reports listed in Table 1, those of Matras and Priesel [14], Davidsohn [8], Weinbaum and Thompson [23], Stibbe [22], Hartwell and Mermod [11] and Mielke [15] described patients who had come to autopsy without operation. In the other eleven cases listed in the table the patients had had the tumor removed surgically and sometimes the thymus gland as well. Among these we find the following results of surgery: One patient who died postoperatively [19]; four patients who had a favorable response immediately after operation; two patients who responded later; and four patients who showed no early response, at least one of whom was followed up long enough to be sure that there would be no late remission of the disease. Humphreys and Southworth [12] apparently cured the aplastic anemia of a young woman by excising her thymoma in 1945. However, she died ten months later of pneumonia, without evidence of agammaglobulinemia. Chediak et al. [6] apparently accomplished a similar cure, but as yet we have obtained no follow-up information on the patient. Chalmers and Boheimer's [3] first patient was treated ineffectually with ACTH; then a thymectomy was performed in 1951 and there was an erythro-

poietic response followed by a relapse. Splenectomy brought about only temporary improvement, but the subsequent relapse was treated effectively with ACTH until the patient's death over two years later from hepatic cirrhosis and siderosis [4]. Chalmers and Boheimer's second patient may have received limited benefit from ACTH therapy prior to surgery. In 1953 a large thymoma on a stalk was removed; the body of the gland was not apparently disturbed [5]. There was no immediate effect from this operation or from a subsequent splenectomy. However, after splenectomy ACTH therapy brought about a return of red cell formation. In 1955 the patient became refractory to all forms of therapy. The question of removing the remaining thymic tissue had not been raised because of the patient's age and other factors. Bakker's [1] patient had a good reticulocyte response to surgery but died three weeks postoperatively of myocarditis. Two patients described by Bayrd and Bernatz [2] and one by Clarkson and Prockop [7] failed to show any early response. The longest recorded follow-up on these three patients is two years, so that a remission, although unlikely, is still possible. Our two patients, reported on by Ross et al. [20], showed no early response at the time they were described. The first patient failed to respond to splenectomy or ACTH therapy; she died of hypogammaglobulinemia and infection without hematopoietic response six years after thymectomy. Ramos' patient also had agammaglobulinemia.

Our second patient had a thymectomy in 1951, performed by Dr. John W. Strieder. There was no response until 1955 when the yearly number of transfusions required dropped from thirty to eleven. In 1956 she required only one transfusion, and since then none. It is not certain whether this is a spontaneous remission or the delayed effect of thymectomy. We are disposed to postulate, however, that if a repressive effect is exerted by the thymus or some other agency upon red cell formation, removal of this agent will not necessarily be followed immediately by bone marrow recovery. This hypothesis might explain the slow response of this patient and, by the same token, other patients could be expected to have a late return of hematopoiesis.

The pathology involved in this problem is an unknown factor. Benign thymic tumors are described in most cases and are probably, as Chalmers [4] has suggested, lymphoepitheliomas. We do not know that these tumors are histo-

logically similar, and we will not know until a single pathologist examines tissue from each. The possibility that thymic tumors affect the bone marrow through the agency of a humoral secretion is another questionable factor. The literature is full of conflicting reports on the effect of thymic extracts upon hematopoiesis in animals [15]. This relationship between tumors of the thymus and refractory anemia is no nearer solution than is that between the thymus and myasthenia gravis. Three of the patients listed in Table 1 (Chalmer's first case, Bakker's patient, and Weinbaum and Thompson's patient) had myasthenia. Wintrobe's patient who had anemia and thymic hyperplasia also had myasthenia.

It has seemed to us that, despite the obscurity of the relationship between thymic tumor and red cell anemia, there was evidence of some connection between the two based upon the course after thymectomy. If such were the case the next logical step would be to remove a roentgenographically normal thymus from a patient with intractable red cell aplasia and observe the results. We found a patient whom we considered to be suitable and performed a thymectomy. The case report follows:

W. S., a white male, married, machine grinder, 57 years of age, first came under our observation at the Massachusetts Memorial Hospitals in August 1953. He had been referred to us by his local physician for a study of a refractory anemia which had been recognized approximately six months previously. His local doctor, whom he consulted because of a rejection by the Red Cross Donor Clinic, discovered his red count to be 2.8 million per cu. mm. Roentgenograms of the gastrointestinal tract revealed no abnormalities. The patient had been placed on a convalescent Sippy regimen. Hematinic therapy was supplied in the form of iron taken orally and frequent injections of liver extract and vitamin B₁₂ which, however, proved to be ineffective. Except for moderate fatigue and exertional dyspnea, the patient was essentially free from symptoms.

His past history and system review were non-contributory except for a potential toxic exposure to benzol in 1945 when he was engaged in demonstrating a vulcanizing machine which entailed frequent and intimate contact with a rubber solvent.

Physical examination on August 11, 1953, gave no abnormal physical findings other than for moderate pallor of the skin and mucous membranes. His hemoglobin was 9.3 gm., red cell count 2.34 million per cu. mm., hematocrit 38 per cent and reticulocytes 2.1 per cent. Results of the Coombs' tests were negative; the erythrocyte osmotic fragility was normal.

His bilirubin concentrations were as follows: conjugated, 0.1 mg. and free, 0.6 mg. per 100 ml. The white cell count was 4,900 per cu. mm. with 35 per cent segmented neutrophils, 21 per cent band forms, 2 per cent basophils, 4 per cent lymphocytes, 11 per cent monocytes, 1 per cent blast forms and 25 per cent unidentified elements. The latter group was comprised of hybrid forms in which characteristics of young lymphocytes, monocytes and plasma cells were combined. The sternal marrow fluid was markedly hypercellular, containing an abundance of immature forms with monocytic features. A pathologic report described the findings as normal. Histologic sections of the clotted marrow were described as "unremarkable." Erythrocyte sedimentation rate (Wintrobe method corrected) was 10 mm. per hour; fasting blood sugar 78 mg. per cent, cephalin flocculation test 3 plus in forty-eight hours; bromsulphalein test showed 4 per cent retention; thymol turbidity was 1 unit. The urinalysis was negative. Repeated stool examinations were negative for hemoglobin. The pH of the fasting gastric contents was 1.9 units. A chest roentgenogram, a barium enema and an upper gastrointestinal series were all within normal limits. On the basis of these observations the patient was considered to have either chronic monocytic leukemia or an unusual maturation deficit involving erythrocytes and leukocytes.

He continued to work as a machinist during the ensuing four years, his hemoglobin maintained between 8 and 12 gm. per cent by means of transfusions. A total of 152 units of red cells was administered between September 1953 and September 1957. Erythrocyte activity was minimal or absent, on the basis of his donor blood requirements and on data from transfusions of labelled red cells, which appeared to exclude a hemolytic component in the pathogenesis of his anemia. Unsuccessful therapeutic trials were carried out with oral folic acid 5 to 15 mg. given daily for six months; ascorbic acid 300 mg. given daily for thirty days; cobalt, in the form of Roncovite,® 30 to 60 mg. given daily for thirty days; pyridoxine hydrochloride, 250 mg. administered intramuscularly in the course of ten days; and vitamin B₁₂ given intramuscularly in 1,000 µg. doses. There was no hematopoietic response to the administration of prednisone in 15 to 30 mg. daily doses, and no beneficial effect was produced by the intravenous administration of 30 mg. nitrogen mustard (0.4 mg. per kilo).

In March 1956, the patient had an exploratory laparotomy because of lower abdominal pain. Biopsy specimens of the liver and of small mesenteric nodes demonstrated marked hemosiderosis, but there was no histologic evidence of malignant disease.

In the spring of 1957 the possibility of a beneficial effect resulting from thymectomy was presented to the patient. He accepted the idea of surgery. The operation was performed on June 6, 1957, and was followed by a brief reticulocytosis which was short-lived. (Fig. 1.)

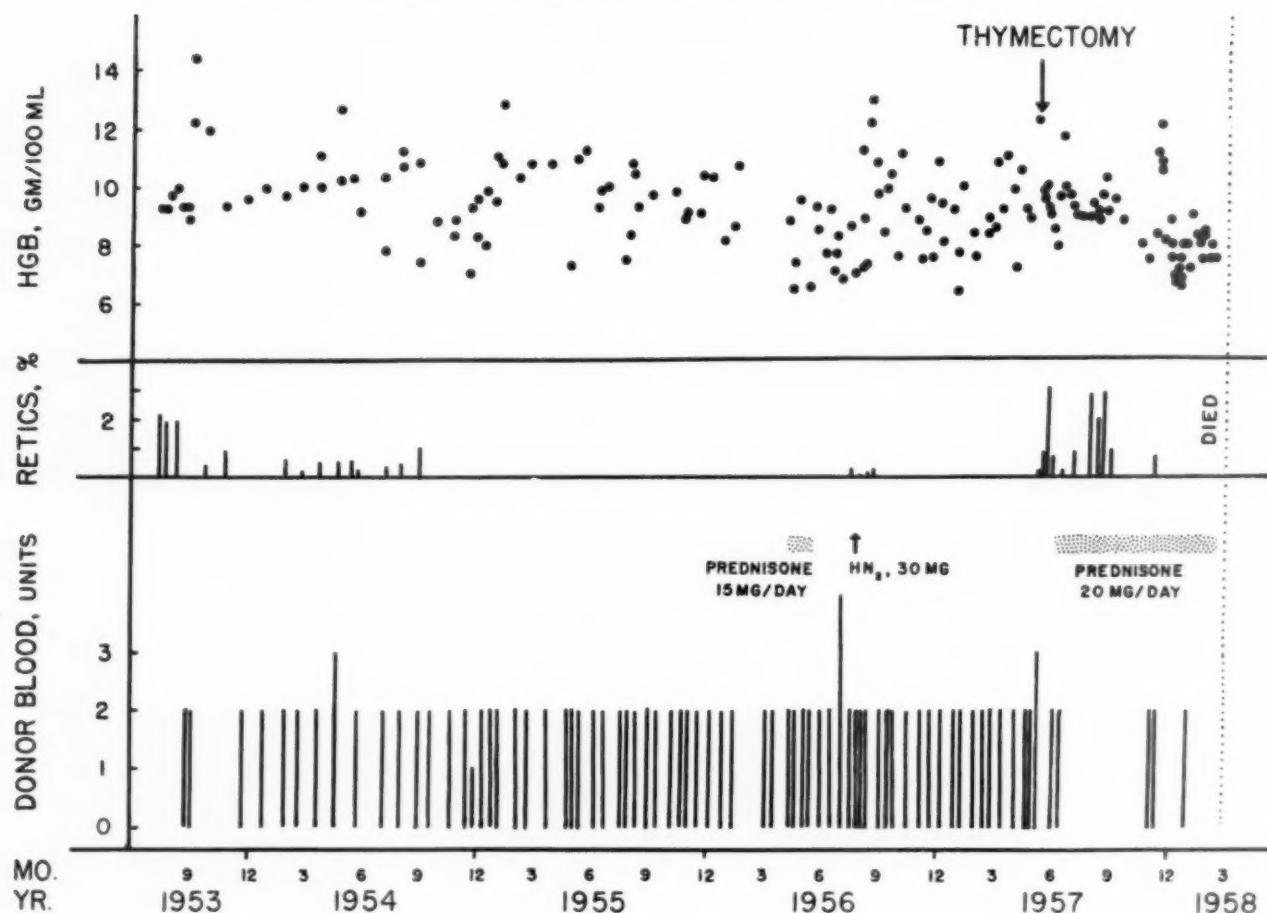


FIG. 1.

The gland weighed 30 gm. (the upper limit of normal weight) and was described as hyperplastic. The bone marrow, examined microscopically, was characteristic of that found in aregenerative anemia but showed no other abnormality. Anemia recurred but, perhaps, progressed more slowly. Four weeks postoperatively (July 5, 1957) prednisone was given orally at a dosage level of 20 mg. daily. Despite the apparent failure of this agent to improve erythropoiesis when given for ten weeks in 1956, prior to thymectomy, the reticulocytes increased on this occasion and the hemoglobin was maintained thereafter at a fairly stable level, i.e., between 9 and 10 gm. per cent with only rare transfusions.

Two months postoperatively the patient's general status deteriorated, partly, it was believed, because of impaired ventilation which was reflected by abnormally large arteriovenous oxygen differences both with and without 100 per cent oxygen inhalation. Electrocardiographic tracings demonstrated coronary sinus rhythm and other evidences of myocardial damage. Chest roentgenograms indicated progressive cardiac enlargement and the development of a pleural effusion on the right lung. Dependent edema became increasingly marked despite digitalization and restriction of dietary sodium to 200 mg. daily. Smears of the

peripheral blood and marrow demonstrated monocytic and histiocytic hyperplasia, interpreted as malignant.

On October 1, 1957, the patient was transferred to the Boston Veterans Administration Hospital where he continued to receive prednisone, 25 mg. daily, and transfusions as indicated in Figure 1. Roentgenograms of the chest began to show densities in the lung fields which were suggestive of "carcinoma." In January 1958, the patient became confused, on one occasion requiring transfer to a closed psychiatric ward with a diagnosis of "paranoid schizophrenia." His mental status improved to the extent that he was able to return home briefly; however, on March 3, 1958, he became extremely weak and returned to the hospital in a deteriorated condition. He did not respond to an increase in steroids to 40 mg. daily. His hematologic status was essentially unchanged. He died on March 7, 1958. Autopsy revealed abscesses of the lung and extensive hemosiderosis. The bone marrow findings were typical of monocytic leukemia.

A comparison of the patient's blood requirements before and after thymectomy suggests that his blood production increased following

operation. During the nine-month period from June 5, 1957 (the day of operation) to March 7, 1958 (when he died) he received 10 units of donor red cells, whereas during the nine-month period immediately preceding thymectomy he received 28 units, and during the preceding nine months, 36 units. His hemoglobin levels during the three nine-month periods were maintained within the same range, as is evident in Figure 1. Additional evidence of increased erythropoiesis may be deduced from the reticulocyte counts which were significantly higher postoperatively. The possibility that steroid therapy may have contributed to or have been responsible for his increased erythropoiesis cannot be excluded.

COMMENTS

In discussing this case with Chalmers in November 1957 we discovered that he had been instrumental in an elective thymectomy performed in a child for pure red cell anemia. A report of this case has subsequently been published [4]. His experience, like our own, offered little encouragement. The patient was a ten month old boy suffering from pure red cell anemia diagnosed at the age of three months. Various medications were employed to stimulate the bone marrow but, except for a small reticulocyte response to the administration of a "growth hormone," only transfusions were of value. At the age of ten months a thymectomy was performed by Mr. A. L. d'Abreu. The reticulocyte count was zero before surgery but rose to 7 per cent after the operation, the highest it had been in the child's life. Normoblasts were present upon marrow aspiration in appreciable numbers upon the thirteenth postoperative day (they had not been found previously). The child subsequently had a relapse and again failed to respond to therapy.

Chalmers' case and our own represent immediate favorable reticulocyte responses (7 per cent in his case, 5 per cent in ours) to thymectomy in the absence of a thymic tumor. Although Chalmers' patient relapsed completely, ours did so only partially because he responded favorably to cortisone therapy with greatly reduced transfusion requirements until the time of his death nine months later. It is unfortunate that in our patient the onset of anemia followed a limited exposure to benzol as it removed him from the group of patients with idiopathic aregenerative anemia. It also is

unfortunate that monocytic leukemia subsequently developed as this throws some doubt upon our preoperative assumption (based upon bone marrow studies) that he was probably not leukemic. Both findings invalidate any conclusions which might be drawn from this case upon the effect of thymectomy in pure red cell anemia.

CONCLUDING REMARKS

Data have been presented from the literature concerning eleven patients with benign thymoma and hypoplastic anemia, and two patients with roentgenographically normal thymus glands but severe aregenerative anemia, who underwent excision of the tumor, the thymus or both. Six patients with thymomas were benefited by surgery: four with an initial erythropoietic response and two with a late one. One patient died postoperatively and the remaining four patients have not been improved. The two patients with elective thymectomy had a good response initially; subsequently one relapsed completely, the other had only a partial relapse which was modified by cortisone therapy but the patient died of monocytic leukemia diagnosed four months postoperatively. Although the influence of the thymus upon the bone marrow is not clear, these results suggest that it would be desirable to conduct further studies on the effects of thymectomy upon patients suffering from refractory anemia.

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Hypophosphatasia in the Adult*

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HYPOPHOSPHATASIA has been known for ten years as a clinical entity occurring in children [1]. Many reports have dealt with children who have been severely afflicted with the disease and have died in infancy. However, others have noted milder forms of the disease in childhood which exhibited progressive improvement over a period of two to three years [2]. If the defect responsible for the disease persists, it is surprising that there have not been more reports of its occurrence or of its residual effects in adults. We are presenting here what we believe to be an example of this disease in two adult sibs in whom we have evidence that the affliction was also present in childhood and was inherited.

CASE REPORTS

CASE I. A forty-two year old woman, a printing machine operator (Maud P.), was seen by one of us (C. E. D.) in 1953 when she was referred for diagnosis to the Royal Society of Medicine by Dr. G. H. Jennings of Edgware General Hospital. At that time no definite diagnosis was suggested but a urine specimen was obtained and analysed chromatographically. A large amount of an amino acid behaving like phosphoethanolamine was found but not then positively identified. By the following year urine specimens from several children with hypophosphatasia had been analysed in this laboratory and it was noted that a large phosphoethanolamine excretion was characteristic and probably pathognomonic of the disease [3-5]. On a periodic review of old chromatograms the identical excretion pattern of urine was noted in the specimen obtained from Maud P., and it became clear that she was probably an adult with hypophosphatasia. It was then arranged to admit her to University College Hospital for metabolic studies.

She was born of a normal pregnancy and weighed 8½ pounds at birth. At first breast fed, she was weaned to cow's milk because of a persistent feeding difficulty which was not completely alleviated until the age of two years. At an unknown age in infancy it was noted that she had bandy legs; rickets was diagnosed and she was treated at Guy's Hospital with cod liver oil, malt extract and ultra-violet light. (Fig. 1.) Light treatment was continued until age

twenty. She did not walk until the age of two and a half, but her legs straightened and she gradually recovered, with only some residual chest deformity remaining. As a child she was fairly well but was never able physically to keep up with other children. Her first teeth decayed rapidly and the second dentition became carious at an early age. By the age of twenty all her teeth had been extracted. At the age of fourteen pain and swelling developed in the right knee. Locking of this joint thereafter occasionally occurred, but a definite diagnosis of dislocated meniscus was never made and she continued to have some intermittent pain and swelling for years. At the age of twenty-one she began to have arthritic pains in the hands and wrists, these were treated with heat and massage with little effect. She continued to work, never entirely free from pain, until the age of thirty-five when minor trauma resulted in a fracture of a metatarsal bone in the right foot. This was placed in a plaster cast and healed very slowly. Three years later severe stabbing pain developed in the left hip radiating down the thigh which was made worse by weight bearing. A roentgenogram revealed a "crack" in the left femur which did not heal completely with six months of orthopaedic treatment supplemented by an unknown dose of vitamin D. With the return of weight bearing the pain recurred, and for the first time a similar pain was noted in the right hip and thigh. The patient also noted occasional aches and pains in the shoulders, back and hands; she later cracked a phalanx in her right foot. At this point she was admitted to the University College Hospital.

The family history revealed the patient to be the third of five children. The first and second were healthy, normal boys, the fifth a healthy girl. The fourth, ten months younger, was a girl who had suffered in childhood from a similar type of "rickets." Her history is dealt with under Case II which follows. The full family survey is to be published in more detail by Dr. H. Harris and his collaborators. As has been found by others, many relatives have low normal alkaline phosphatase levels. In addition, Harris has shown that many excrete small quantities of phosphoethanolamine in the urine [6].

Examination of Maud P. revealed a woman of short stature (57½ inches) and normal body proportions (crown to pubis 29 inches, pubis to heels 29 inches, span 57¾ inches). Her weight was 44 kg.

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FIG. 1. CASE I. Taken at age seven while the patient (Maud P.) was receiving ultra violet ray treatment for "rickets." Note Harrison's sulci and rickety rosary.

There was some deformity of the skeleton with a prominent sternum and clavicles, Harrison's sulci and mild costochondral enlargements. There was no frontal bossing; the lumbar spine was lordotic with a limited range of anteroposterior movement. The thoracic spine was unusually straight. (Fig. 2.) There was slight forward and lateral bowing of both femurs and there were well localized points of bony tenderness at the junction of the upper and middle thirds of these bones. There was an early cataract of the right eye but no calcification or blue scleras, and the discs were not pale. The blood pressure was 90/60 mm. Hg. Chvostek's and Troussseau's signs were negative, as was further examination of the nervous system. There were no other physical abnormalities.

Laboratory examinations included the following: haemoglobin, haematocrit, erythrocyte sedimentation rate, white blood cell count, all normal. Sodium, 145 mEq./L.; potassium, 4.6 mEq./L.; carbon dioxide, 104 mEq./L.; calcium, 10 mg./100 ml.; phosphorus, 4.6 mg./100 ml.; magnesium, 2.16 mg./100 ml.; alkaline phosphatase, 2.9 King-Armstrong units; acid phosphatase, 2.5 King-Armstrong units. The blood urea was 27 mg./100 ml.; urea clearance, 101%; urine sediment, normal; concentration and dilution test, specific gravity 1.002-1.023. A urinary amino acid chromatogram showed a glycine pattern

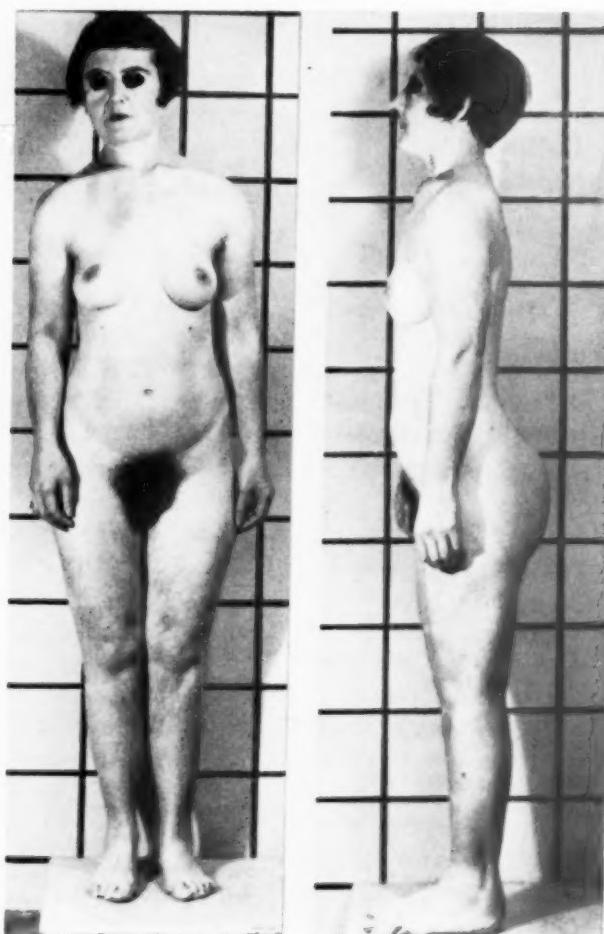


FIG. 2. CASE I. Note prominent sternum and straight thoracic spine, features also characteristic of the child cases of hypophosphatasia.

(normal), and in addition a strong phosphoethanolamine spot. This pattern has been reproduced on every subsequent specimen. Plasma electrophoresis was normal.

Radiological examination revealed a minor degree of rarefaction throughout the skeleton. The main findings which were clearly responsible for most of her symptoms were the fractures of both femurs at the junctions of the upper and middle thirds of the shafts. (Fig. 3.) Exocallus formation around these fractures was minimal, but there was much endocallus. No fractures were noted elsewhere, but there were some interesting changes in the shape of the bones. The skull was small and round (Fig. 4), with a "copper-beaten" appearance. The thoracic cage was normal in size but the chondral ends of the ribs were grossly enlarged, as if there had been severe rickets in childhood without sufficient opportunity to remodel the bones subsequently. (Fig. 5.) Lack of remodelling was also noted at the ends of some of the long bones. The tibias, for instance (Fig. 6), were flask-shaped at their proximal ends. The vertebral bodies were of normal shape, the thoracic spine (Fig. 7) being



FIG. 3. CASE I. Roentgenogram of pelvis. Note ectopic calcification and fractures in both femurs.

unusually straight. The bones were otherwise of apparently normal structure with no suggestion of the changes found in other metabolic diseases such as osteomalacia or hyperparathyroidism.

An additional finding visible on the roentgenograms was the presence of a considerable degree of ectopic calcification around the joints and tendon attachments to bone. This is perhaps best seen in the region of the ischia and femoral heads (Fig. 3), and in the intervertebral ligaments. (Fig. 7.)

CASE II. Kathleen C., a forty-one year old housewife, sister to Maud P., was seen because she was said to have suffered "rickets" as a child and to have been treated at the same time as her sister. (Fig. 8.) She recovered from this illness and has remained well since. However, she had lost her primary dentition early and all her teeth by the age of nineteen because of a "lack of proper enamel," and she had been



FIG. 4. CASE I. Roentgenogram of skull.

advised to have her children by Caesarian section because of a small pelvis. She is otherwise active and well.

Examination revealed a weight of 36.5 kg., a height of 57½ inches and a span of 58 inches, with normal body proportions. There was a slight pallor of both optic discs. The chest was deformed by the presence of a protrusive sternum and Harrison's sulci. The thoracic spine was unusually straight. The skeleton was otherwise normal except for a slight inward bowing of both tibias but there was no genu valgum. Further examination was within normal limits, except for evidence of a healed chronic

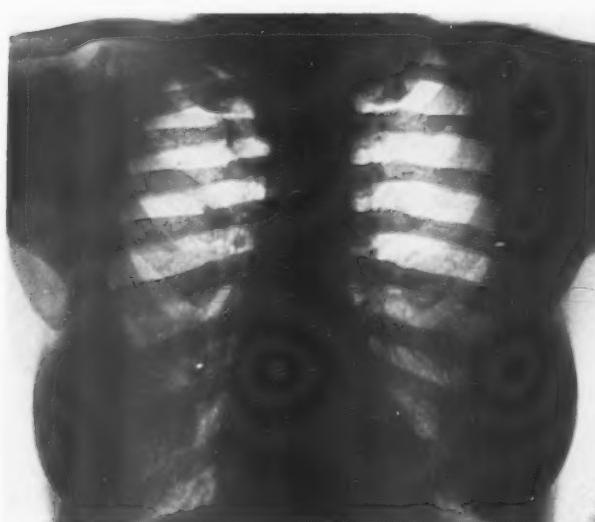


FIG. 5. CASE I. Roentgenogram of chest. Note particularly the expanded anterior ends of ribs.



FIG. 6. CASE I. Roentgenogram of knees. Note Erlenmeyer flask shape of the proximal ends of the tibias.



FIG. 7. CASE I. Roentgenogram of thoracic spine. Note its straightness, squaring of the vertebrae with calcification of intervertebral ligaments.

mastoiditis. Her plasma alkaline phosphatase was 1.5 King-Armstrong units, and her urinary chromatogram had the same abnormal phosphoethanolamine spot as was found in her sister's (Maud P.) chromatogram.

Radiological examination revealed changes in her bones identical to those found in her sister Maud. Only two features differed from those already mentioned, namely, there were no fractures in her femurs or other bones, and the ectopic calcification, while definitely present and distributed in the same manner, was much less advanced. To illustrate the remarkable resemblance between the two sisters, her chest roentgenogram is shown in Figure 9.

She has a son, aged eight, who is of normal stature and enjoys excellent health. His plasma alkaline



FIG. 8. CASE II. Taken at age six while the patient (Kathleen C.) was receiving ultra violet ray treatment for "rickets." Note the remarkable resemblance to her sister shown in Figure 1. This resemblance continues to the present date.



FIG. 9. CASE II. Roentgenogram of chest. Note remarkable resemblance to Figure 5.

phosphatase is 8.5 King-Armstrong units; a value below normal for this age.

She has remained in good health to the time of writing.

METABOLIC STUDIES AND FOLLOW-UP
OF CASE I

Metabolic balance data for calcium and phosphorus, and alkaline phosphatase levels before and during treatment with vitamin D₃, vitamin D₂ and cortisone, are shown in Figure 10. An attempt was also made (not shown here) to demonstrate possible changes in plasma calcium levels coincident with induced changes in plasma phosphorus. This was done by giving orally a solution of 20 gm. of neutral sodium phosphate for twelve days, followed by 120 ml. of aluminum hydroxide suspension (6.6 per cent) daily for twelve days. No changes in plasma calcium were observed coincident with phosphorus values ranging from 3.1 to 6.8 mg./100 ml. It is to be noted that plasma phosphorus has always been somewhat elevated in this patient while plasma calcium has always been normal. Throughout this period there was no demonstrable objective improvement in balance data or in roentgenographic appearances, and no subjective change was noted by the patient. The main features of the calcium and phosphorus balances are that she is in balance for both calcium and phosphorus, and that a slightly greater than the normal proportion of both calcium and phosphorus is excreted in urine, with less in the faeces. This resembles the excretion pattern following a mild overdose of vitamin D. Renal clearance studies (not included here) have shown that the raised plasma phosphorus is entirely due to over-absorption of phosphorus from the diet and not at all to a lowered renal clearance.

This treatment produced no obvious improvement in the patient and she was then treated with stilbestrol (0.25 mg./day) and aluminum hydroxide (120 ml./day), and followed in the Out Patients Department. Further treatment over varying periods, including a diet low in vitamin D, the administration of methyl-testosterone, vitamin A, cortisone and small doses of calciferol, did not alter the clinical, biochemical or radiological aspects of the disease. The plasma alkaline phosphatase has always remained between 1.2 and 3.5 King-Armstrong units.

Eight months following discharge this patient was admitted to the Royal National Orthopaedic Hospital, where a "drilling" of the affected area of the left femur was performed by Mr. J. I. P. Jones on January 7, 1957. When weight bearing

was resumed six months later the pain in the femur had greatly lessened and has since disappeared. This procedure was performed because of the remarkable effect Macey [7] reported in two similar cases in which osteotomy was performed, and in a further case kindly described to us by Dr. Henneman [8]. The rise in plasma alkaline phosphatase noted by Macey following this procedure was not duplicated in our patient.

Her clinical state has slowly worsened. She now complains of migratory aches and pains in multiple bones. In May 1958, a roentgenogram revealed a fracture of the fifth rib on the right under an area of somewhat more severe pain than normal. No trauma had been noted. The fracture is gradually improving under conservative treatment.

COMMENTS

The clinical data from our two patients strongly suggest that they have hypophosphatasia, the same disease as is now well described in the paediatric literature. Not only had they both in childhood manifested clinical signs similar to those of "rickets," from which they had made spontaneous recoveries, but they had both had dental defects producing early loss of primary and secondary dentition. In addition, they both have small skulls with a "copper-beaten" appearance as seen on roentgenograms, and one sib has pale optic discs, all of which we consider evidence of some increased intracranial pressure in childhood. Their present body build and roentgenograms are also consistent with what one would expect from healed survivors of childhood hypophosphatasia.

The biochemical studies also support this suggestion since, as one would expect from an inherited condition, they are exactly the same as in the disease of childhood. Not only have they low plasma alkaline phosphatase levels (this finding is not too specific, as it may occur in other diseases and the normal range of levels is widely scattered) [9,10] but they also have a large constant excretion of phosphoethanolamine in the urine. This finding has been present in all fourteen patients with child hypophosphatasia whose urine specimens have been submitted to Dr. H. Harris and ourselves for analysis. It has also been found in nine of the ten urine samples in which it was looked for in the cases quoted by Fraser [2]. The only exception (his Case 29) is reported as having renal insufficiency, a situation which we would expect to

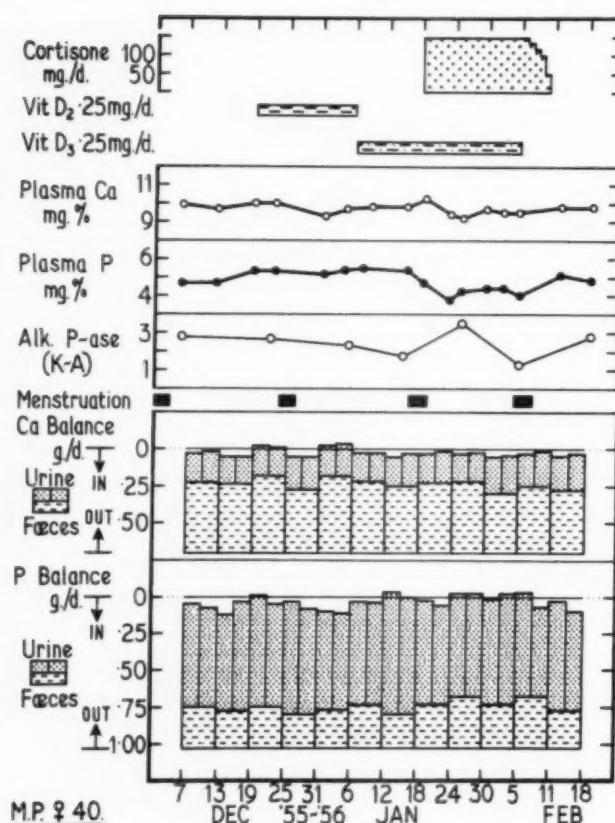


FIG. 10. CASE I. Metabolic data. Calcium and phosphorus balances are charted according to the usual conventions of Albright and Reifenstein [27].

decrease greatly the phosphoethanolamine excretion. The identification of the latter compound, originally only by chromatographic methods, has now been confirmed by Cusworth [17]. He used a urine specimen from our patient (Maud P., Case 1) for this purpose.

Further evidence in support of the view that the same disease exists in our adult cases as occurs in childhood comes from our preliminary study of the family, which has shown that other relatives have low normal plasma alkaline phosphatase levels and a slight degree of phosphoethanolaminuria. Our genetic studies, published in a preliminary form, of thirteen families in which there were child cases show the same features [6].

These two sisters present many similarities to the two brothers described by Macey [7] under the title of "multiple pseudofractures." He also noted low plasma alkaline phosphatase levels, and considered whether or not this was concerned in the pathogenesis of the disease. Dr. Henneman has also kindly sent us details of an adult case which shows many similarities to ours.

This has not yet been reported in detail but was Case 35 quoted by Fraser [2].

The theoretical implications of this further study of hypophosphatasia are of some interest. Ever since the early work of Robison [12], alkaline phosphatase has been implicated as a key enzyme in bone formation. It is difficult to reconcile this view with the existence of mild cases of hypophosphatasia and of the recovery of originally severe cases since this occurs in the presence of a continuing low plasma enzyme concentration. Moreover, postmortem studies have also shown that only small quantities of alkaline phosphatase are present in the bones of afflicted subjects [1,13]. It is true that most children with hypophosphatasia suffer from bony abnormalities during the stage of rapid growth. It is clear, however, that those who do not die of some complication, such as high cerebrospinal fluid pressure from premature fusion of cranial sutures, or of renal damage presumably from prolonged hypercalcaemia, do survive and would be expected to attain adult life in reasonably good health. Indeed, one of the two sisters we have described here is clinically normal and has had one child. The reason for the development of spontaneous fractures and tender bones in the other sister remains obscure. It was thought that a clinical as well as a biochemical comparison between them might provide an important clue as to the reason for the adult complications. As the latter had more marked signs of ectopic calcification and had chosen a diet which contained more vitamin D, and as she liked sunbathing (her healthy sister being quite different in all these respects), we thought that the precipitating cause of her recent bone troubles might have been an oversensitivity to the vitamin D in her environment. This seemed to be confirmed by the calcium and phosphorus balance data. (Fig. 10.) This was the reason she was treated with cortisone, which we believe in certain instances may have an antivitamin D action [14,15], and with a diet low in vitamin D. It was unfortunate for this theory that, although the metabolic studies showed a calcium metabolism similar to that observed in a patient who had received a slight overdose of vitamin D, our attempts to improve our patient's condition failed dismally. As an admission of our therapeutic despair we recently began to give her moderate doses of vitamin D. This treatment is being discontinued as it seems to have coincided with a worsening of her condition and an

increase in her ectopic calcification. We must recall that children with hypophosphatasia frequently have hypercalcaemia; some of them have also been rather unexpectedly easily intoxicated with vitamin D, suggesting that they were oversensitive to it. It is of interest that infants with the syndrome of "idiopathic hypercalcaemia" may also have low plasma alkaline phosphatase levels, thus mimicking the plasma levels in hypophosphatasia [16]. However, these infants neither excrete phosphoethanolamine in the urine, nor (unless very severe) do they have bone disease.

It is of some interest to consider the cause of the phosphoethanolaminuria. Its presence in our adult cases suggests strongly that this is a lifelong phenomenon in hypophosphatasia, provided of course that the kidneys remain undamaged. Phosphoethanolamine is readily hydrolysed by alkaline phosphatase and it is possible that it is indeed one of the natural substrates for this enzyme in human tissues. If so, a decrease of alkaline phosphatase would be expected to lead to an accumulation of phosphoethanolamine in the body, which would then overflow into the urine, as has actually been found in hypophosphatasia [17]. Whatever the immediate explanation may be, the phosphoethanolaminuria would seem to be of great diagnostic value.

We have unfortunately no suggestions to make for the treatment of this disease. In the childhood cases no improvement has been reported following the administration of vitamin C, thiamine, sodium citrate, growth hormone, thyroid extract, testosterone, oestrogens or probenecid. The administration of vitamin D has given rather ambiguous results. Recently cortisone therapy has been reported to have a salutary effect on the radiological appearance of bone, the low serum alkaline phosphatase and the elevated serum calcium in a hypophosphatasic child on several occasions when it was administered [18]. This favourable report has been confirmed [19] and denied [20]. We also gave cortisone to our patient independently and for a different reason, but there were no changes either clinically or biochemically except for a rather interesting slight rise in plasma alkaline phosphatase. (Fig. 10.) It is difficult to interpret these findings, which seem contradictory to those of Fraser. It may be relevant that the degree of the bone changes in childhood appears to be dependent upon the rate of growth.

It is possible, therefore, for the cortisone to produce apparent healing radiologically because it has had the effect of reducing growth rate and not for any more specific reason. It is fortunate that the orthopaedic treatment of the adults described by Macey [1] and by Henneman [8] gave excellent results. This encouraged us to attempt to interfere with the fracture in the femur of our patient, with possibly some alleviation.

SUMMARY

Two sisters are presented, now aged forty-one and forty-two, whom we think represent adult survivors of hypophosphatasia, a disease hitherto only described in children. Both sisters had had "rickets" in childhood, from which they had made a spontaneous recovery. The elder is now crippled because of fractures and painful bones, the other remains symptom free. They both constantly manifest a low alkaline phosphatase level in the plasma and a large excretion of phosphoethanolamine in the urine, as in the childhood disease. Studies of the relatives who all have normal bones, show that minor degrees of both these biochemical features frequently occur among them. Metabolic studies of the elder sib have shown results consistent with a mild degree of an overdose of vitamin D. However, this condition was largely uninfluenced by the administration of small doses of vitamin D, cortisone, and a diet low in vitamin D.

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Hepatolenticular Degeneration*

Clinical, Biochemical and Pathologic Study of a Patient with Fulminant Course Aggravated by Treatment with BAL and Versenate

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DURING the past decade, expanding knowledge of the biochemical abnormalities of hepatolenticular degeneration has provided some rationale for treatment. Increased deposition of copper in the brain and liver [1,2], increased copper and amino acid excretion in the urine [3,4] and abnormal serum copper transport due to a deficiency of a metalloprotein, ceruloplasmin [5-7], have been repeatedly demonstrated in patients with the disease. As it is generally believed that the major clinical manifestations are due to the deposition of copper in the tissues, therapeutic approaches have been directed chiefly at eliminating the excess tissue copper with chelating agents. Dimercaprol (BAL) has been most widely used with some favorable results [8] and some equivocal responses [9,10]. Calcium disodium ethylenediaminetetraacetic acid (versenate) and more recently, dimethylcysteine (penicillamine) [11] have also been used.

The following case is of interest for several reasons. The clinical course was marked initially by mental symptoms, later by major convulsions with focal electroencephalographic abnormality and terminally by a fulminant febrile course apparently precipitated by treatment with BAL and versenate. The liver exhibited an acute and subacute toxic necrosis which followed therapy and probably was a complication of treatment.

CASE REPORT

A twenty-three year old Filipino man was admitted to the Veterans Administration Hospital, Palo Alto, on March 22, 1957, for treatment of a progressive neurological disorder.

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† Present address: Southern Pacific Hospital, San Francisco, California.

‡ Deceased.

According to the patient, his first signs of illness began in May 1954 while he was on active duty with the Marine Corps. He was admitted to the U. S. Naval Hospital, Oakland, California, because of blurred vision, stiff legs and dizziness. In July 1954 he was discharged from the Marine Corps with the diagnosis of schizophrenic reaction and multiple sclerosis. Twelve electroconvulsive treatments were used in treating his mental disorder. He next entered the Veterans Administration Hospital, Los Angeles, California, where he remained for fifteen months. Soon after leaving this hospital he was arrested for burglary and sent to prison. While in prison he had difficulty in walking, was tremulous and complained of double vision. He was transferred from prison to the Veterans Administration Hospital, Oakland, California, on February 11, 1957. During his stay there he was found to have a spastic gait, slurred and explosive speech, a positive Romberg sign, hyperactive but equal reflexes and impulsive behavior. His short stay at this hospital was marked by considerable deterioration. Drooling developed and he had difficulty in swallowing which resulted in several episodes of severe choking. A characteristic Kayser-Fleischer corneal ring was discovered just prior to his being transferred.

The patient was born in New York City but lived in many different places because of a disrupted family life. Although the mother was presumed to be living, the patient had had no contact with her since the age of twelve. His father died in 1950 from what appeared to have been cirrhosis of the liver associated with alcoholism. The father never suffered from any neurological disease akin to the patient's. There were no other children of these parents. The patient had enjoyed excellent health until the onset of his present illness.

Physical examination on admission to the Veterans Administration Hospital, Palo Alto, revealed the fol-

lowing noteworthy findings. The patient was a young, muscular man who was immobilized in a wheel chair because of marked ataxia. His nutritional state was good. He drooled, grimaced and showed evidence of emotional lability with an occasional period of forced laughter. His trend of thought was coherent but his memory appeared to be defective. Except during episodes of forced laughter, he appeared apathetic with his head hanging down and his trunk wobbling as he sat in his chair. No definite delusions or hallucinations could be elicited. The vital signs were normal. No skeletal abnormality of the head or neck was found. The pupils were equal and reacted promptly to light and accommodation. Extraocular movements were normal and without nystagmus; however, convergence was limited and double vision was produced by this maneuver. A characteristic yellow-green iridescent Kayser-Fleischer ring was seen along the margin of each cornea. At some points the ring showed typical duplication. The optic discs were normal. Marked dysarthria with slurred speech and some drooling was present. The facial muscles were rigid even in repose giving his face a taut and expressionless appearance. Sensory functions were well preserved. Marked muscle hypertonicity was present in all the skeletal muscles. The increased muscle tonus was slightly greater on the left side than on the right. The muscles of the trunk were so rigid that the trunk moved as a single unit without any evidence of flexion. There was marked truncal ataxia. Walking could be attempted only with support. The steps were broad-based and made with no sense of sureness. In the standing position he tended to fall backward. From a sitting position he tended to drift to the right side. The finger-nose test, using the left upper extremity, was marked by terminal tremor, but on the right side the test was performed rather well. The same was true of the heel-knee test, with evident dysmetria on the left side and better function on the right. A definite pronator sign could be observed on the left side. All deep tendon reflexes were considerably increased but bilaterally equal. Cremasteric reflexes were present, but abdominal reflexes were absent. The Hoffmann sign was negative. The left great toe was constantly held in an extended position without any stimulus being applied. The right great toe showed a positive extensor response with the slightest stimulation to the sole.

Extensive laboratory studies were performed on this patient. The numerous blood counts were all normal except for a slight leukocytosis terminally. Urinalyses revealed intermittent albuminuria of 1 to 2 plus but no other abnormality. Determinations of blood creatinine, glucose, sodium, potassium, chloride, calcium and phosphorus were normal. Serum uric acid levels were low, values of 1.9, 2.6 and 1.9 mg. per 100 ml. being reported. Several series of hepatic tests were performed. The serum bilirubin, alkaline phosphatase and bromsulphalein retention were always

within normal limits. The serum proteins were also normal except for a steadily decreasing level of albumin (to 3 gm. per 100 ml. on June 11, 1957) associated with failing nutrition. The cephalin flocculation test was 4 plus at forty-eight-hours. The highest thymol turbidity level was 6.5 units. The prothrombin time varied between 56 and 84 per cent. The serum cholesterol was slightly elevated ranging between 292 and 302 mg. per 100 ml.; the esterified fraction ranged between 68 and 72 per cent. Examination of the spinal fluid revealed only borderline total protein values of 43 and 46 mg. per 100 ml. The electrocardiogram was normal. An electroencephalogram taken on May 1, 1957, showed a slow wave focus in the left frontal area as well as generalized slowing. (Fig. 1.) Roentgenograms of the chest, skull, thoracic and lumbar spine, hips, elbows, knees and abdomen revealed no abnormalities.

Initially the mental state of the patient was characterized by emotional lability with periods of depression. He improved slightly on treatment with 200 mg. of chlorpromazine daily. On April 24, 1957, he experienced a typical grand mal seizure followed within a few hours by a second seizure. On the following day he had a number of minor seizures which were manifested by twitching movements of the extremities and face. He was started on Dilantin,® 0.4 gm. given daily, which controlled the seizures well.

The course of his illness was rapidly progressive. Treatment with dimercaprol was decided upon after attempts to obtain dimethylcysteine were unsuccessful. This course of treatment was started with 200 mg. intramuscular doses given twice daily every other day from May 4 to May 16. (Fig. 2.) By May 10 he was having a febrile response to each administration of dimercaprol. With the injection on May 12 the temperature reached a peak of 104°F. (40°C.) By May 14 his temperature peaked at 105°F. and again on May 16. Following this latter dose, treatment was discontinued for the next several days and he became afebrile. On May 16, 1957, a generalized papulo-erythematous rash resembling a typical drug eruption developed; this cleared during the next several days while administration of the drug was discontinued. The injection of dimercaprol on May 21 was accompanied by a rise in temperature to 104°F. In addition to the fever, mental depression with stupor, increased difficulty in swallowing and increased generalized muscle tonus were also present.

In view of this unfavorable response to the use of dimercaprol a course of intravenous calcium disodium ethylenediaminetetraacetic acid was planned. He received the first injection of 5 ml. (1 gm.) of versenate intravenously on May 28, 1957. At the time the injection was being made he had already begun to chill, so his subsequent febrile responses may not have been due to this drug. He received repeated injections on May 30 and 31, June 1, 4 through 7, 10 through 14 and 17. This course of treatment did not appear to

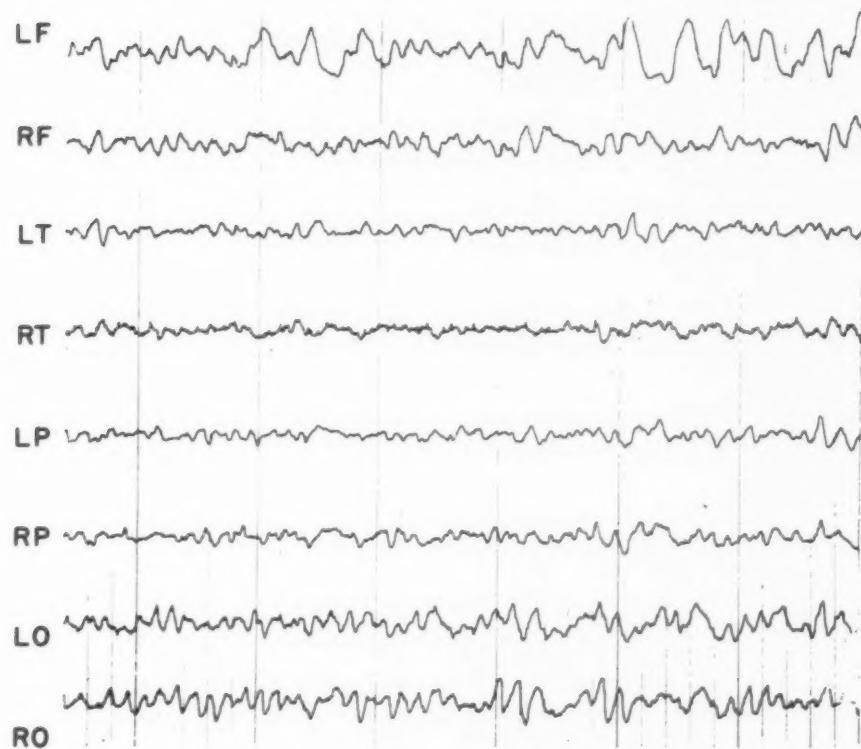


FIG. 1. Electroencephalogram. Slow wave (2-3/s) focus in left frontal area.

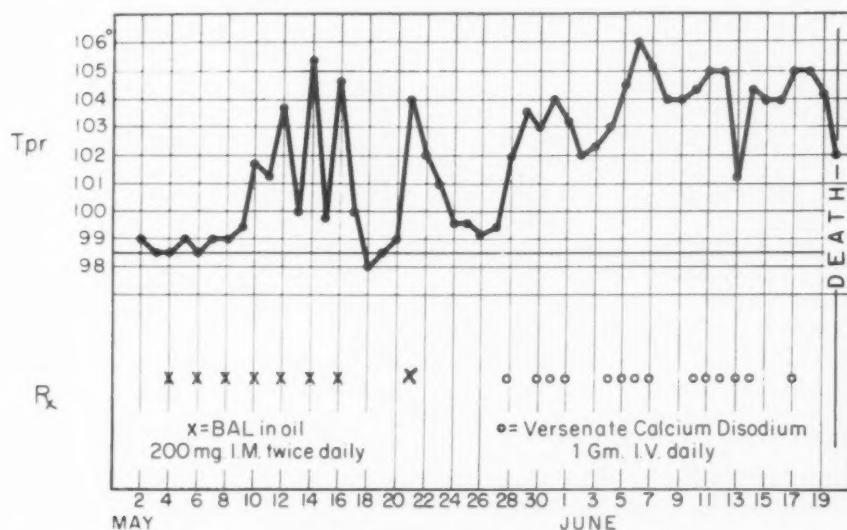


FIG. 2. Apparent exacerbation of febrile course by therapy with dimercaprol. No abatement with versenate treatment.

help him at all. Biochemical measurements made prior to and following each course of treatment are tabulated in Table I.

A constantly recurring fever was noted during this period and continued for the remainder of the patient's life. Because of the prolonged fever the possibility of a concurrent disease was considered. Repeated roentgenographic examinations of the chest failed to demonstrate lung disease, especially miliary tuberculosis. Numerous blood cultures and several

smears for malaria parasites were also negative. A downhill course of fever, increasing neurologic signs, progressive nutritional impairment and increasing stupor continued without remission until the patient's death on June 20, 1957.

At autopsy the body weighed 140 pounds and measured 67 inches. Pigmented rings (Kayser-Fleischer) were visible in the limbus of each cornea. No icterus of sclerae or skin was detected.

The liver weighed 1,200 gm. and felt moderately

TABLE I
BIOCHEMICAL FINDINGS BEFORE AND DURING TREATMENT WITH BAL AND VERSENATE

Date (1957)	Plasma		Urine				
	α -amino N (mg./100 ml.)	Copper Oxidase [12] (% transmission)	Volume (ml./24 hr.)	Total N (gm./24 hr.)	α -amino N (mg./24 hr.)	Creatinine (mg./24 hr.)	Copper (μ g./24 hr.)
<i>Control.</i>							
4/20	...	99
4/23	3.2	87	1,540	12.1	261	1,232	...
4/28	...	89	1,040	344 (33 μ g. %)
5/2	...	93
<i>BAL</i>							
5/22	...	95	685	830 (80 μ g. %)
5/23	920	16.2	115	975	...
<i>EDTA</i>							
6/13	4.0	89	1,635	14.7	153	850	640 (50 μ g. %)
Normal values	4-6	40-50% at 530 m μ	150	...	12-110

firm. External and sectioned surfaces were diffusely nodular, the nodules varying from 2 to 10 mm. in diameter. Fine, retracted fibrous septums measuring no more than 1 mm. in thickness separated the nodules.

The brain weighed 1,300 gm. Coronal sections revealed a discrete lesion in the subcortical white matter of the left frontal lobe parasagittally. This lesion extended 5 cm. anteroposteriorly from the level of the genu of the corpus callosum to the level of the mammillary bodies and measured 2 by 1.5 cm. It presented a characteristic spongy appearance and was retracted from the surface encroaching at times on the underlying deep layers of the cortex. The globus pallidus showed brown discoloration bilaterally. There was no gross atrophy of either globus pallidus or putamen. A few spongy foci were noted anterior to the splenium of the corpus callosum. The dentate nuclei were distinctly atrophic and brown. A small, vaguely outlined spongy lesion was noted in the white matter of the left cerebellar hemisphere near the cortex. The upper third of the spinal cord showed no gross lesions.

The lungs weighed 350 gm. each, the lower lobes being hyperemic. The spleen weighed 250 gm. The testes were small but otherwise normal. The adrenal glands were normal in size. Examination of the other organs, including the kidneys, revealed no significant changes.

Spectrographic analysis of liver tissue revealed the copper content to be ten times that of normal liver [13]. A large amount of copper was also reported

in the brain. Using the reagent biscyclohexanone-oxalyldihydrazone, colorimetric demonstration of large amounts of copper in chopped liver tissue and approximately one-tenth that amount in chopped brain tissue, putamen and dentate nuclei was possible. Tissue specimens of the liver from several patients with portal cirrhosis of the Laennec type, examined with the same technic, gave a negative colorimetric reaction for copper.

Sections of the liver exhibited widespread irregular lobular distortion and scarring of a multilobular variety. (Fig. 3.) Portal areas were often connected and irregularly widened by fibrosis, proliferation of small bile ducts and cellular infiltration. Some of the central veins remained; a number were eccentric. The parenchyma was dotted with multiple zones of necrosis which were often extensive and tended to be situated centrilobularly. (Fig. 4.) In most of the necrotic zones the liver cells were intensely eosinophilic, anuclear and rounded. A dense infiltration of frequently smudged polymorphonuclear leukocytes was seen between the necrotic cells. In other focal areas of subacute necrosis the liver cells had disappeared and the collapsed stroma was dotted with fairly numerous phagocytes containing golden iron negative pigment, presumably lipofuscin. (Fig. 5.) The parenchyma also showed coarse to fine fatty vacuolization, regenerating hepatic cells and intense venous congestion.

Sections of the kidneys revealed occasional fibrosed glomeruli scattered through the cortex, generally associated with a few atrophic tubules and an inter-

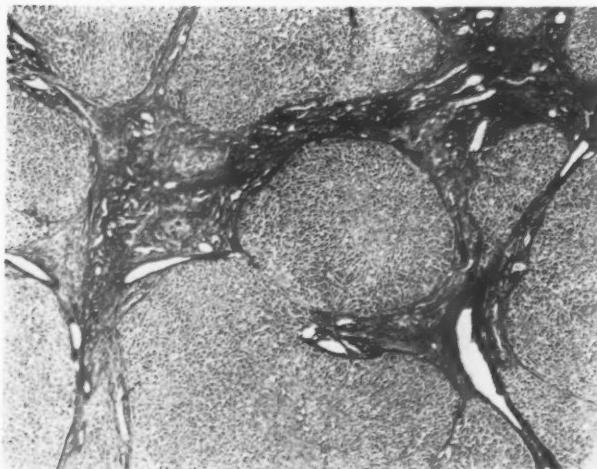


FIG. 3. Cirrhosis, liver, portal, multilobular. Hematoxylin-van Gieson $\times 20$.

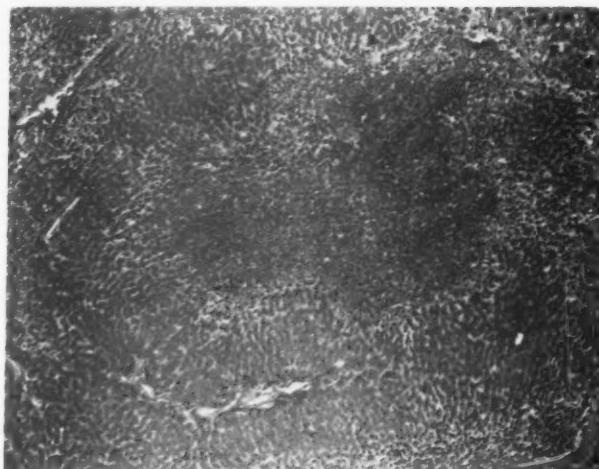


FIG. 4. Necrosis, hepatic, centrolobular, acute. Hematoxylin and eosin $\times 42$.

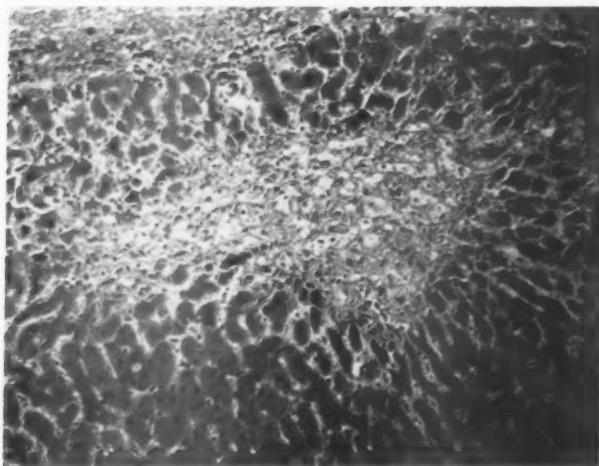


FIG. 5. Necrosis, hepatic, subacute. Hematoxylin and eosin $\times 120$.

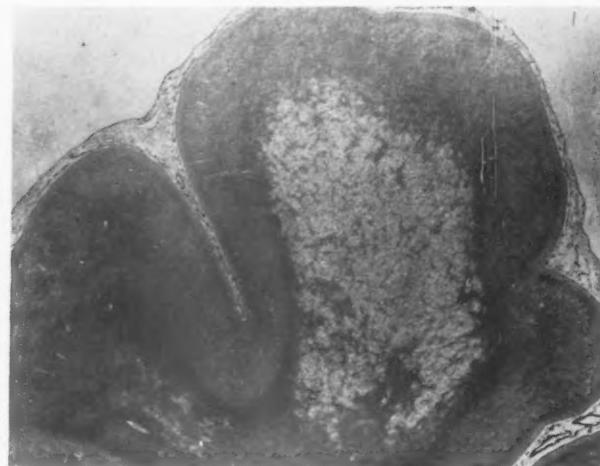


FIG. 6. Cortex, left frontal lesion. Hematoxylin-van Gieson, $\times 6.5$.

stitial lymphocytic infiltration. Protein debris was not infrequently present in the capsular spaces. Tubular changes were widespread and fairly severe. The epithelium of the proximal convolution was often swollen and had an irregularly festooned luminal border; the lumens contained considerable pale granular protein debris. Similar changes were much more prominent and numerous in scattered segments of the distal nephron.

Sections of the brain revealed disseminated lesions with a characteristic spongy appearance. These were predominantly in the following areas: (1) subcortical white matter tending to encroach on the cortex (Fig. 6); (2) putamen-pallidal (lenticular) region with more severe change in the former than in the latter; (3) substantia nigra; and (4) dentate nucleus. The most severe lesions showed gross vacuolization of the tissue with variable, scant to moderate glial reaction. The latter was in the form of gitter cells or astrocytes, many of which were atypical in form with little tendency to fiber production. In less vacuolated areas

(Fig. 7) diffuse microglial and/or connective tissue response was evident. Occasionally cells containing phagocytized particles were noted within the lesions, usually in the perivascular spaces. Their granular deposits stained blue-black with cresyl violet, suggesting copper, but failed to stain in rubanic acid preparations, possibly because the fixed tissue was unsuitable. Within the lesions and more diffusely scattered were occasional atypical glial forms with either enlarged nuclei or homogeneous oval bodies suggesting a degenerative form of Alzheimer glia. (Fig. 8.) In the substantia nigra, melanin pigment was being phagocytized by cells. In and about the dentate nucleus unusually extensive gliosis had occurred. There were no changes in the brain stem, upper third of the spinal cord or optic pathways.

The sections of lung exhibited acute and chronic hyperemia, focal edema and bronchopneumonia of the aspiration type. Mild fibrocongestive alterations and scattered lipid granulomas were noted in the spleen. The adrenal cortex had undergone moderate

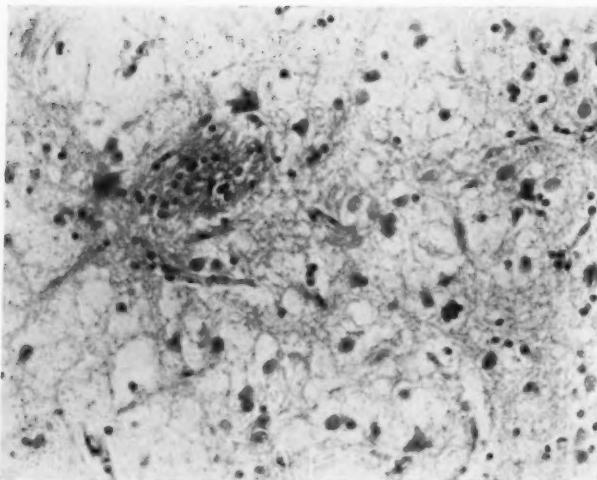


FIG. 7. Putamen. Status spongiosus with glial reaction. Hematoxylin-van Gieson $\times 315$.

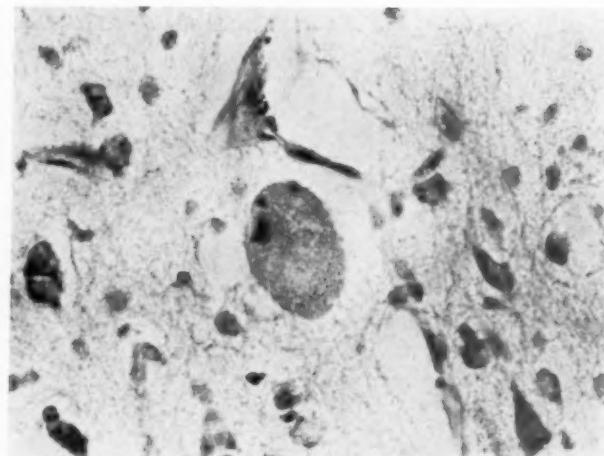


FIG. 8. Cortex. Alzheimer glia. Nissl $\times 700$.

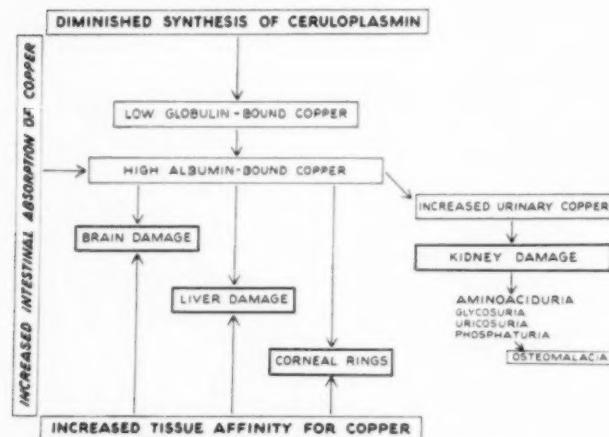


FIG. 9. Principal metabolic defects in Wilson's disease.

degenerative changes. In the testes seminiferous tubules showed almost no spermatogenic activity. No significant alterations were noted in any of the other tissues.

The principal pathologic diagnoses were: (1) Hepatolenticular degeneration (Wilson's disease) with (a) portal cirrhosis, (b) brain lesions characterized by status spongiosus and Alzheimer glia affecting predominantly the left frontal subcortex, lenticular nuclei, substantia nigra and dentate nuclei, (c) pigmentation of the corneal limbus (Kayser-Fleischer ring), bilateral; (2) necrosis of the liver, centrolobular, acute and subacute, toxic; (3) glomerulonephritis, late acute diffuse proliferative and latent chronic; (4) bronchopneumonia, aspiration type.

COMMENTS

Many of the characteristic clinical features of hepatolenticular degeneration were present in this case. The association of a disorder of motor coordination with the pathognomonic corneal ring adequately established the diagnosis. How-

ever, certain features were distinctive. Mental signs preceded the neurologic signs early in the disease. Although a concurrent functional psychiatric disorder could not be ruled out, variable behavioral changes have been frequently described in this disease [14].* The occurrence of major seizures is also known, but rarely has it been possible to correlate the focal electroencephalographic abnormality so well with the local brain lesion. The prominent cerebellar signs in this patient could have led to diagnostic confusion had other clinical features not been present. The clinical and laboratory signs of liver disease were slight. Extensive liver disease is known to occur with only minor deviations of hepatic tests from normal, suggesting the need for liver biopsy in doubtful cases. Although hepatolenticular degeneration may run a febrile course in juvenile cases, in the present case the close association of fever with the use of dimercaprol (as well as the concomitant allergic skin rash) and later with verenate suggests that these drugs were responsible, at least in part, for the fulminant termination.

The gross and histopathologic lesions in the liver and brain were characteristic of hepatolenticular degeneration. The multinodular cirrhosis was consistent with the classic descriptions. However, the acute and subacute necrotic lesions in the liver suggested a toxic etiology. Although they might possibly be attributed to severe nutritional deprivation imposed on a previously damaged liver, the adverse clinical reaction to dimercaprol closely coincided with the apparent chronologic onset of these lesions. Early toxic-

* We have since observed another case presenting as a schizophrenic reaction. Treatment with penicillamine effected a complete psychiatric remission.

logic studies of the effects of dimercaprol in rats and rabbits with liver injury due to carbon tetrachloride suggested increased toxicity to dimercaprol in the presence of liver damage [15]. While many clinical reports have mentioned a variety of reactions to the administration of dimercaprol, including drug eruptions and fever, no mention of liver necrosis has been made [16]. No record of toxic reactions to versenate has been found in the literature. Nevertheless, the acute centrolobular hepatic lesions in this case probably developed while versenate was being administered. The subacute lesions were chronologically compatible with treatment with dimercaprol. Thus we believe that the hepatic necrotic lesions were initiated in a previously damaged liver by the injections of dimercaprol and were further aggravated by the ensuing treatment with versenate.

Although the brain lesions in hepatolenticular degeneration are commonly believed to be localized, in part due to the emphasis by Wilson of this point, they are frequently disseminated. In this case the subcortical white matter, dentate nuclei and substantia nigra were affected in addition to the lenticular nuclei. The lesions were characteristic histologically, exhibiting status spongiosus and Alzheimer glia. Anatomic localization of these lesions correlated unusually well with the clinical manifestations, including seizures and cerebellar signs.

Current concepts of the biochemical lesions of hepatolenticular degeneration are summarized in Figure 9. Our patient showed decreased levels of ceruloplasmin (copper oxidase), increased urinary excretion of copper, increased copper in the tissue of the liver and brain, aminoaciduria with normal plasma amino acids and decreased levels of serum uric acid. Although the urinary excretion of copper was increased following treatment with dimercaprol and sodium versenate, any possible beneficial effects were masked by the adverse reaction to the treatment. Concomitant with the increased excretion of copper, the aminoaciduria decreased. This decrease occurred despite a normal and stable level of plasma amino acids and an increased total urinary nitrogen excretion, suggesting that aminoaciduria is a reversible phenomenon. The ceruloplasmin deficiency appears to be fixed, showing no change from this treatment. Deficient synthesis of ceruloplasmin is probably the basic metabolic derangement in hepatolenticular degeneration.

APRIL, 1960

SUMMARY

A case of hepatolenticular degeneration with several unusual features is reported. Clinically, the course was marked by insidious onset with mental symptoms, later by major seizures with focal electroencephalographic abnormality, and terminally by fever and an allergic skin rash. Biochemical studies revealed the usual abnormalities found in this disorder with a marked diminution of ceruloplasmin, hypercupriuria, increased copper in tissue and aminoaciduria. Pathologic study revealed disseminated brain lesions which correlated well with the clinical picture of multiple system involvement.

Of special interest was the finding of acute and subacute hepatic necrotic lesions. These lesions were chronologically related to the period of treatment with dimercaprol (BAL) and calcium disodium ethylenediaminetetraacetic acid (versenate). The use of these drugs also coincided with the acute febrile terminal course. Both the adverse clinical response and the toxic hepatic lesions appeared to have been aggravated or precipitated by the drug therapy.

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Pulmonary Thromboarteritis Associated with Interatrial Defect and Rheumatic Carditis*

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SCLEROSIS and dilatation of the pulmonary arteries are regularly found in association with functionally patent interatrial defects. Generally these dilated arteries remain patent until death but in fifteen of the reported cases massive thrombosis of the extrapulmonary portions of the main pulmonary arteries was found. In 1953 Canada, Goodale and Currens [1] first recognized this combination of lesions as a fairly distinctive clinical and pathological entity.

The initial symptom of severe and progressive respiratory distress usually begins late in life and often in persons who have never had cardiac symptoms previously. X-ray films disclose enlarged pulmonary arteries associated with hypertrophy of the heart. At necropsy, the main common pulmonary artery to the bifurcation and the intrapulmonary branches are patent. The main right and left trunks from the bifurcation to the hilus of the lungs are dilated and filled with yellowish grey, slightly translucent, friable and sometimes laminated thrombi similar to those found in old aortic aneurysmal sacs. The lumen of the vessels is greatly narrowed but not completely occluded. The lungs, although markedly engorged with blood, seldom contain discrete infarctions.

Canada, Goodale and Currens [1] reported three such cases and cited four others [2-5]. Four of the sixty-two cases of interatrial cardiac defect collected by Roesler [6] in 1934 appear to have had similar thrombotic occlusion of the pulmonary arteries. Additional cases that fall into the same category are those of Wahl and Gard [7], Trounce [8], Rosenthal [9], and one of the ten cases described by Bedford, Papp and Parkinson [10].

Intimal plaque formation, dilatation and alterations in blood flow probably favor the

formation of thrombi in the pulmonary arteries, but since the latter do not develop in the great majority of cases of interatrial cardiac defects or of pulmonary hypertension due to other causes, it seems likely that other factors may play a role. The purpose of the present report is to describe another case, the sixteenth, of thrombosis of the pulmonary arteries associated with patent interauricular septum that corresponds in almost all respects to those previously reported. In the present case, however, the wall of the pulmonary arteries in the areas of thrombosis was the seat of a diffuse inflammatory reaction which was indistinguishable histologically from the rheumatic lesions of the left auricle described by Mac Callum [11] and of the ascending portion of the aorta as described by Pappenheimer and Von Glahn [12]. That this inflammatory process may, in fact, be rheumatic is supported by the finding of definite rheumatic lesions in the myocardium and mitral and tricuspid valves. It is suggested that the inflammation of the vessel walls may have incited the formation of thrombi.

It is well known that valvular lesions are frequently found in association with interatrial septal defects. When frank mitral stenosis is present the case is classified as Lutembacher's syndrome. In Roesler's sixty-two collected cases there were valvular deformities in forty-one and in thirty the mitral valve was involved. It is generally conceded that the gross appearance of the damaged valves is indistinguishable from that of healed rheumatic valvulitis [13]. In some instances, as in the reports of Bedford et al. [10] and Espino-Vela [14], these valvular lesions have been classified as rheumatic. Other authors have considered the possibility that these lesions are associated congenital malformations or that they are secondary to the mechanical effects of altered blood flow within the heart caused by the

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FIG. 1. Left auricle with large interauricular defect.



FIG. 2. Thrombus in dilated right main pulmonary artery.

interatrial septal patency. In almost none of the reported cases is the distinctive lesions of rheumatic disease, such as myocardial Aschoff bodies and valvular verrucae described. It is obvious that even if the valvular lesions are rheumatic in nature, inflammatory activity is absent or meager at the time of necropsy in these cases.

If the valvular alterations associated with interatrial septal defects are, in fact, the results of rheumatic endocarditis, this would strongly suggest that the mixing of the left and right auricular blood through such an opening renders the heart extraordinarily vulnerable to the rheumatic process.

CASE REPORT

The patient was a sixty-eight year old man who was admitted to the New York Veterans Administration Hospital because of progressive dyspnea and cough for three years' duration. Initial x-ray films of the chest disclosed a right hilar mass that was thought to be a neoplasm. Subsequent x-ray films showed a gradual enlargement of this mass. At the age of sixteen he was said to have had an attack of rheumatic fever, and a cardiac murmur was detected at the

time of induction into the Army in 1918. He had arrhythmic palpitations for the past five years and had been digitalized continuously during this time. Thirty-eight years ago he was treated with Salvarsan® for syphilis.

On examination he was hoarse, coughing, and in respiratory distress. There was some midscapular pain on breathing and loud respiratory wheezes were heard in this area. A prominent precordial heave and a thrill was felt in the apical region. The point of maximal cardiac impulse was in the sixth intercostal space in the left posterior axillary line. The ventricular rate was more rapid than the pulse rate and the rhythm was irregular. A loud systolic and a questionable presystolic murmur were heard at the apex. The second aortic and pulmonic sounds were equal and were not split. On palpation the liver was enlarged. The left pupil was pinpoint and did not react to light and accommodation. An iridectomy for cataract had been performed on the right eye two years previously. The blood pressure was 120/86 mm. Hg, pulse 100 beats per minute, temperature 99.6°F.

The erythrocyte count was 6,780,000 per cu. mm. and the hemoglobin 20.9 gm. per 100 ml. The erythrocyte sedimentation rate (Wintrobe) was 4 mm. per hour. The hematocrit was 61 per cent. A 2 plus reaction and an anticomplementary Kolmer reaction were revealed by serological tests for syphilis. The

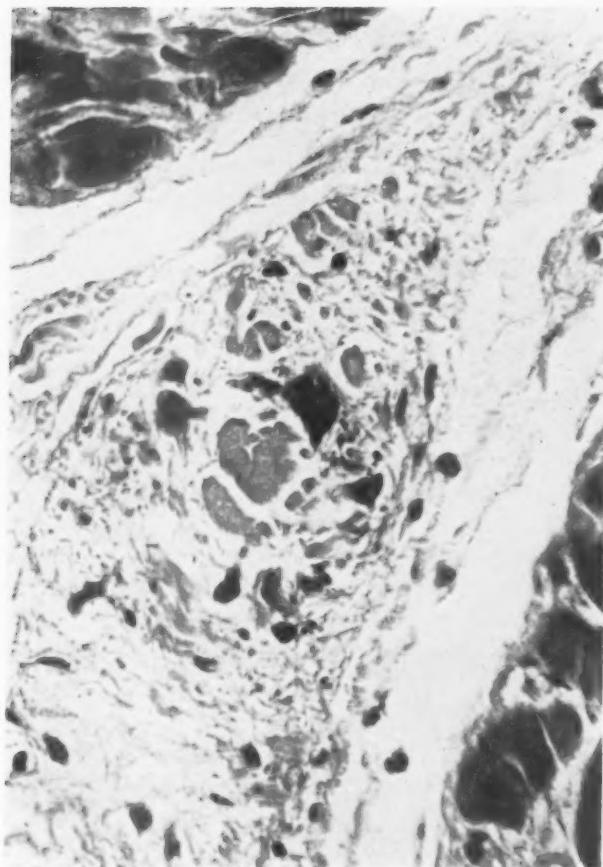


FIG. 3. Aschoff body in interventricular septum.

serum CO_2 was 24 mEq./L. The other laboratory data on admission were not significant.

X-ray film of the chest on admission revealed an enlarged heart and markedly dilated pulmonary arteries. The findings were interpreted by Drs. G. Kaplan and L. R. Lawrence of the Radiology Service as indicative of congenital heart disease, probably an interauricular septal defect. Electrocardiographs two days later showed atrial tachycardia, incomplete AV block with multiple dropped beats, right bundle branch block and probable digitalis toxicity.

The patient's condition remained unchanged until the sixth day when he coughed up bright red blood and became progressively cyanotic and anoxic. He was given oxygen and anticoagulants were administered. On the eighth day the venous pressure was 80 mm. H_2O and the Decholin® circulation time was thirty-two seconds. He became febrile. The antistreptolysin titer on the ninth day was less than 100 units. Additional hemoptysis and a fall of blood pressure to 90/54 mm. Hg occurred on the thirteenth day. The prothrombin time was thirty-one seconds (control thirteen seconds). Later that day the blood pressure fell to shock levels and he died. The clinical diagnoses were pulmonary embolism and congenital heart disease (Lutembacher's syndrome).

At necropsy, examination was restricted to the

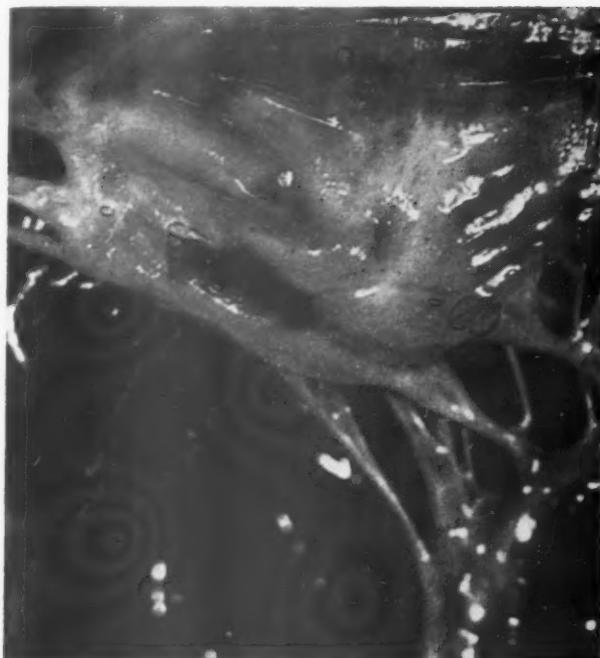


FIG. 4. Verrucous endocarditis of the tricuspid valve.

thoracic organs. The heart weighed 625 gm. Its enlargement was due chiefly to dilatation and hypertrophy of the right auricle and ventricle. The membranous septum (septum secundum) of the fossa ovalis was lacking and a large circular opening, about 3 cm. in diameter, joined the two auricles. (Fig. 1.)¹⁴ The large right auricle had a thickened endocardium. The leaflets of the tricuspid and mitral valves were thickened and slightly rounded at their free margins. This change was more pronounced in the tricuspid than in the mitral valve. Neither valve was grossly deformed, asymmetrical or calcified. The dilated tricuspid valve ring measured 14.5 cm. No other significant changes were noted in the heart.

The thoracic aorta was small in size and freely elastic. It contained a few small intimal plaques but there was no evidence of syphilis.

The main pulmonary artery was dilated but its intimal surface was smooth. Beginning at the bifurcation, the extrapulmonary portions of both major pulmonary arteries were filled with hard, dense, firmly adherent yellowish grey or red thrombotic masses that almost completely occluded the lumens. (Fig. 2.) These extended for some 12 to 15 cm. in length and were 2 to 4 cm. in thickness. Portions of the thrombi could be scraped away as irregular crumbly granules. The thrombi resembled those frequently seen in aneurysmal sacs but were not distinctly laminated. Beyond the thrombi the pulmonary arteries were very sclerotic and contained innumerable intimal plaques most of which were hyalinized. Linear intimal grooving was not noted.

The main bronchial arteries were not conspicuously dilated. The ductus arteriosus was obliterated. The lungs were engorged with blood throughout and

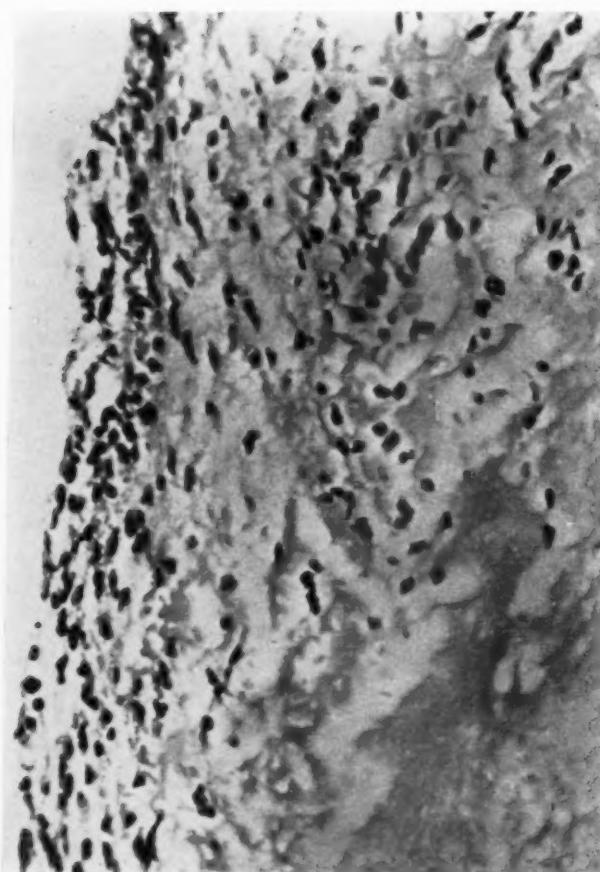


FIG. 5. Tricuspid endocarditis showing cellular infiltration and necrosis of collagen.

had a hemorrhagic appearance. The lower lobes were poorly aerated, but there were no well defined infarcts. The bronchi were filled with bloody mucus and were lined by hemorrhagic mucosa.

Microscopic examination revealed a diffuse increase of interstitial connective tissue throughout the myocardium, but there were no large scars. In addition, small numbers of characteristic Aschoff nodules were found in several sections. (Fig. 3.) They were most numerous in the apical region of the interventricular septum. The mitral valve leaflet was thickened and hyalinized. At the bulbous distal extremity was a large plaque of calcium. Adjacent to this the connective tissue contained many small capillaries, but there was no cellular infiltration and no verrucae. An area of erosion and hemorrhage was found on the auricular aspect of the tricuspid valve at the line of closure. (Figs. 4 and 5.) The collagen at the edges of this gap was swollen and deeply eosinophilic. Large mononuclear cells were found here and at many other points within the substance of the valve. The foci of cellular infiltration were most pronounced just beneath the surface endothelium. Although no protruding verrucae were found, the collagen in the areas of cellular infiltration was homogenous, afibrillar and deeply eosinophilic.

The medial coat of the major pulmonary arteries

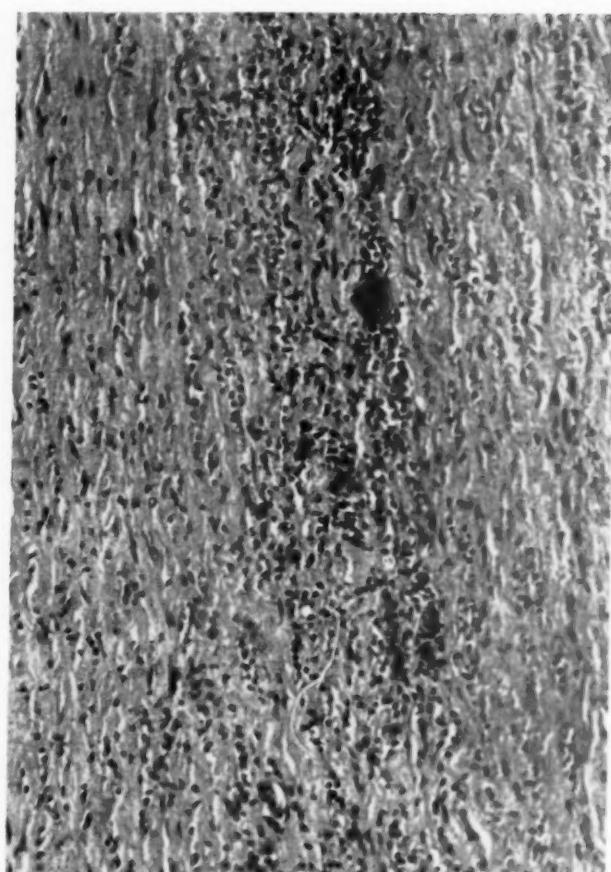


FIG. 6. Diffuse cellular infiltration in media of thrombosed pulmonary artery.

beneath the thrombi was greatly disorganized in numerous sections. The smooth muscle cells were disrupted and obliterated by a dense infiltration of leukocytes with elongated, pyknotic nuclei. (Fig. 6.) These nuclei resembled those of polymorphonuclear leukocytes but were very irregular in shape. They resembled very closely the bizarre cells described in rheumatic auriculitis. (Fig. 7.) They were most numerous in the middle third of the media. In places they formed palisades against swollen, pink-staining collagen bands. (Fig. 8.) This feature also resembled very closely the endocardial lesions seen in rheumatic auriculitis [11]. In elastic tissue stains there was extensive disruption of the elastic lamellae many of which were reduced to small torn fragments or granules. The adventitia of the arteries was thickened by dense masses of collagen in which many perivascular accumulations of lymphocytes were found. The thrombi consisted of compact masses of hyalinized acellular fibrin. They were united to the intima by narrow zones of proliferating connective tissue.

The intrapulmonary branches of the pulmonary artery and the arterioles showed severe sclerotic changes but no evidence of inflammation. The intima of these smaller arteries was irregularly thickened and hyalinized. The intimal plaques contained very little lipid and no calcium. The media of these vessels was

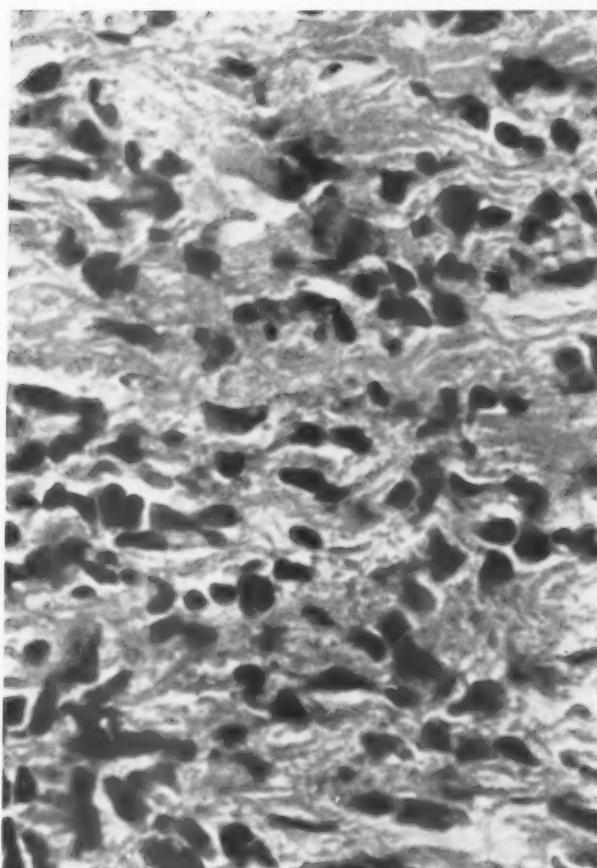


FIG. 7. Infiltration of leukocytes with distorted hyperchromatic nuclei in media of pulmonary artery.

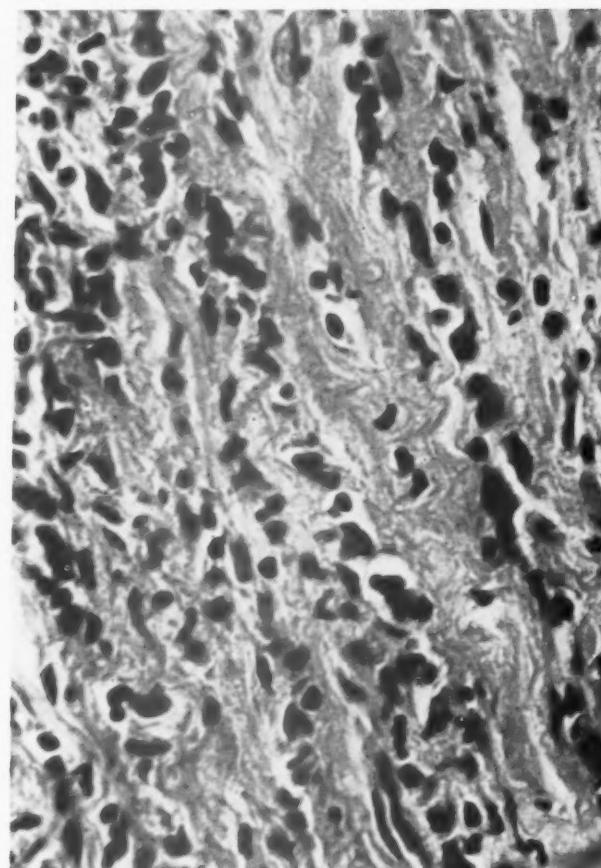


FIG. 8. Palisade arrangement of nuclei against swollen collagen band in media of pulmonary artery.

thin but for the most part intact. The pulmonary alveoli were filled with extravasated erythrocytes and in a few places the alveolar septa showed signs of early necrosis. The alveolar capillaries were not engorged and there were few pigment-laden heart failure cells in the alveolar sacs. The submucosal vessels of the bronchi were extensively engorged.

No evidence of syphilitic change was noted in sections of the thoracic aorta. The media was delicate, almost hypoplastic, but the continuity of the smooth muscle and elastic lamellae was not impaired. No evidence of inflammatory change was noted either in the delicate adventitia or in the media.

COMMENTS

Arteritis of small pulmonary vessels is sometimes seen in association with rheumatic heart disease [15]. It is seldom found in the absence of mitral stenosis and marked passive venous engorgement of the lungs. Braunstein [16] and Johnstone and Smith [17] believe that these lesions are related to increased intrapulmonary arterial pressure and are analogous to the lesions of periarteritis nodosa. Acutely inflamed arteries are found in the lungs in cases of severe mitral

stenosis even when no active rheumatic lesions are found in the heart. Old and Russell [18] found necrotizing pulmonary arteritis in a case of congenital heart disease with patent interventricular septum and pulmonary hypertension. There is some evidence that hypertension may play a role in the localization of the lesions of systemic periarteritis nodosa [19]. However, inflammatory reactions of large elastic arteries, such as were present in our case, have not been described in periarteritis nodosa.

Brenner [20], in a comprehensive survey of all lesions involving large pulmonary arteries, describes briefly two cases of rheumatic pulmonary arteritis. The changes he observed do not resemble those found by us very closely. We have found no other reports of rheumatic lesions of the large pulmonary arteries.

In one of the three cases reported by Canada, Goodale and Currens [1] a diffuse, moderately severe, acute and chronic inflammatory reaction was found within the media and adventitia of the pulmonary artery in the region of the thrombi. The nature of this change was not

discussed and it was not considered to be rheumatic, possibly because no rheumatic lesions were identified in the heart.

There was no evidence of syphilis in this case. This is of interest because some of the features of the process suggest a luetic etiology and in our case there was serological evidence of syphilis. The adventitial fibrosis and lymphocytic infiltration and the rupture of medial elastic fibers are very similar to changes found in syphilitic aortitis. In our case there was no inflammatory lesion in the aorta. Furthermore, there were no gummatous foci and the intense infiltration of cells resembling distorted polymorphonuclear leukocytes and palisading of nuclei against swollen collagen bands is more indicative of rheumatic than of luetic inflammation.

In the case reported by Wahl and Gard [7] an inflammatory lesion was found in the wall of the thrombosed arteries which was considered to be analogous to that of syphilitic arteritis. This patient was a nineteen year old girl, the youngest in the series of sixteen cases, and had a negative Wassermann reaction. In two of the four cases reported by Roesler [6] inflammatory reactions were noted in the walls of the thrombosed arteries. It is possible that the inflammatory lesions found in five of the sixteen reported cases have the same etiology.

It should be noted that many of the lesions of rheumatic fever occur at sites that are subjected to unusual mechanical trauma, as in joint tissues and at the line of closure of valve leaflets. Rheumatic left auricular lesions seldom develop in the absence of severe mitral stenosis. There is some evidence that subcutaneous nodules can be made to form artificially at areas that have been mechanically injured [21]. The rare examples of rheumatic aortitis have been associated with marked deformity of the aortic valve and occur in areas where "impingement" plaques are found later in life in cases of calcareous aortic stenosis. These areas are believed to represent points against which are directed narrow streams of blood discharged through the orifice of the stenotic valve.

The severe degree of mechanical strain imposed on the pulmonary arteries in cases of interatrial septal defect as evidenced by the marked dilatation and sclerosis, when associated with the rheumatic state, may favor the localization of the rheumatic process at this atypical site.

It should also be noted that small numbers of

Aschoff bodies may be found in the hearts of adults many decades after the last attack of rheumatic fever. This was stressed by VonGlahn and Pappenheimer [22] in 1935 and has received renewed attention recently by the finding of Aschoff nodules in surgically amputated auricular appendages obtained at mitral commissurotomy from persons in whom no clinical sign of rheumatic activity can be elicited [23]. If active rheumatic inflammatory reactions can occur in the hearts of such persons there is no reason why they should not occur elsewhere and especially in relation to interatrial septal defects, if the presence of this malformation increases susceptibility to rheumatic lesions.

A mild infiltration of polymorphonuclear leucocytes is sometimes found in the stretched but otherwise normal media of pulmonary arteries the lumens of which have been obstructed by impacted emboli a few hours before death. If pulmonary embolism does not cause death until several days have elapsed, this acute inflammatory reaction is no longer found. Nevertheless, assuming that this reaction is a result of embolic impaction, its intensity would depend upon the force with which the embolus is lodged in the lumen of the vessel. This would probably be relatively intense in cases of pulmonary hypertension. The possibility must therefore be considered that the thrombotic masses found in association with interatrial defects are embolic in origin, and that the mesarteritis results from direct mechanical injury to the vessel wall.

The vast majority of thrombi found within pulmonary arteries are embolic rather than of local formation. However, none of the authors who have described pulmonary thrombi in cases of interatrial septal defect considered them to be of embolic origin. We also believe that the thrombi found in our own case formed locally within the pulmonary arteries. The reasons for this are the following: (1) the thrombi themselves are very different in appearance and structure from the usual embolus and have obviously been present in the vessels for a considerable period; (2) they often show distinct lamination suggesting that they form as parietal thrombi in a succession of layers; (3) the lumen of the vessel although greatly reduced in size is usually not completely obstructed; (4) massive sudden embolization of this extent would under most circumstances cause immediate death; (5) limitation of the area of thrombosis to the

segment extending from the bifurcation to the hilum of the lung suggests the presence of some local intramural factor in the formation of the thrombi.

SUMMARY

A case of large interatrial defect, asymptomatic until late in life, is reported. The terminal illness was characterized by respiratory difficulties and was due to massive thrombosis of the main pulmonary arteries from the point of bifurcation to their entrance into the lungs. The clinical diagnosis was established by roentgenographic examination of the chest. A small group of cases with similar clinical and pathological findings have been described previously by others. In the present case an inflammatory process was found in the wall of the thrombosed arteries. The histological features of this reaction were very similar to those sometimes found in the endocardium of the left auricle in association with severe mitral stenosis and less often in the proximal portion of the aorta. It is suggested that the lesion in the pulmonary artery is rheumatic in nature and this is further supported by the finding of characteristic Aschoff nodules in the myocardium and active rheumatic valvulitis of the tricuspid leaflets. It is also suggested that the altered pathway of blood flow through the interatrial defect, changes in pulmonary blood volume and tension as well as rate of flow render the pulmonary artery vulnerable to this unusually located rheumatic reaction and that the inflamed vessels are secondarily occluded by thrombi.

Acknowledgment: We are indebted to Dr. Frank J. Lovelock, Chief, Pulmonary Disease Service, for permission to present the clinical data and wish to thank Mr. Robert Waldek for preparing the photomicrographs.

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Primary Hyperaldosteronism without Adrenal Tumor*

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MORE than twenty well described cases of primary hyperaldosteronism have been reported [1-17]. Most of these, including Conn's original case, have been associated with a neoplasm of the adrenal cortex, usually a benign adenoma. This report concerns a young patient with the clinical syndrome of hyperaldosteronism who was found at surgery to have adrenal glands of normal appearance. Studies of aldosterone excretion showed an initially high value with a further apparent increase during adrenocorticotropic hormone administration. Balance studies demonstrated a large storage of potassium during a preoperative phase of massive potassium therapy, correcting the hypokalemic alkalosis. The importance of this as part of the preparation for surgery will be discussed. It appears that this patient may represent a distinctive type of hyperadrenalinism occurring early in life.

CASE REPORT

A. P., an eighteen year old girl, was admitted to the University Hospitals on September 25, 1957, because of hypertension noted during a routine college entrance physical examination. Since the age of ten occasional episodes of muscle spasm and tightness or weakness of the arms and legs had occurred. These episodes recurred three or four times a year and lasted for one or two days. During one episode the patient was unable to attend school because of inability to walk.

The patient first learned of an elevated blood pressure at fourteen years of age. This was noted several times subsequently, but the condition was not treated. At the time of admission to the University Hospitals the patient admitted that she had had occasional frontal headaches associated with nervous tension, stiffness in the calf muscles after walking a long distance, polyuria, polydipsia and nocturia. The

menses had been regular since thirteen years of age. Both the mother and maternal grandmother had a history of hypertension.

Physical examination revealed a robust, healthy appearing girl who weighed 146 pounds and was 65 inches tall. The blood pressure was 240/160 mm. Hg, but following a period of bedrest was 210/140 mm. Hg. During measurement of the blood pressure, carpal spasm occurred. The Chvostek sign was not present. There was mild, generalized narrowing and sclerosis of the retinal vessels. The remainder of the physical examination was within normal limits.

Initial laboratory data revealed the hemoglobin to be 14 gm. per cent, the leukocyte and differential counts were normal. There were 293 eosinophils per cu. mm. The urinalysis revealed 1-plus albuminuria, pH 7, occasional white cells, and 1 plus casts (non-specified). An Addis count showed 653,000 casts, 2,170,000 white blood cells, and 3,420,000 red blood cells in a twelve-hour period. The urine specific gravity reached 1.016 on a concentration test. The blood urea nitrogen was 16 mg. per cent.

Chemical examination of the blood revealed a serum carbon dioxide combining power of 42 mEq. per L., serum chloride 93 mEq. per L., serum sodium 151 mEq. per L., serum potassium 2.0 mEq. per L., serum calcium 10.2 mg. per 100 ml., serum phosphorus 3.5 mg. per 100 ml., serum total protein 7.0 gm. per 100 ml. and normal albumin and globulin concentrations. An oral glucose tolerance test revealed a fasting blood sugar of 70 mg. per 100 ml. with a rise to 98 mg. per 100 ml. in a half hour and 73 mg. per 100 ml. in two and a half hours. There was no fall in blood pressure after the administration of Regtine.®

The urinary aldosterone by the method to be described was 22 µg. per twenty-four hours (upper normal, 10 µg. per twenty-four hours).† The urinary 17-ketosteroids were 10 mg. per twenty-four hours

† Dr. V. R. Mattox of the Mayo Clinic kindly carried out a determination of urinary aldosterone by his method at this time and found a value of 23 µg. per twenty-four hours.

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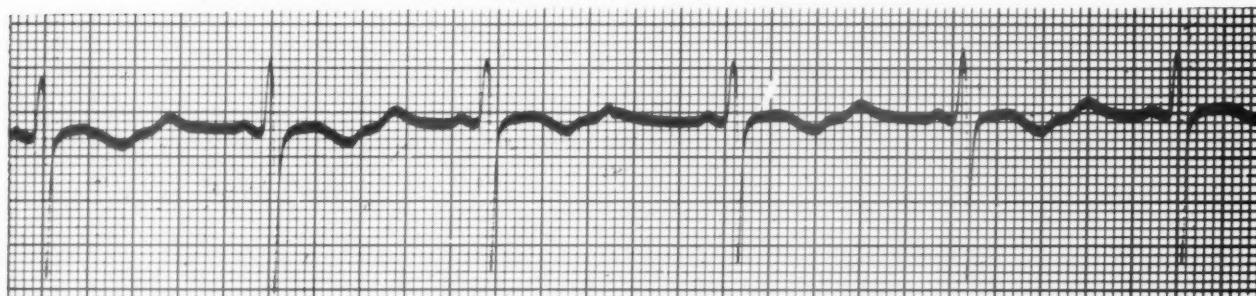


FIG. 1. Initial V₃ electrocardiograph lead illustrating U wave and inverted T wave of hypopotassemia.

and the urinary 17-hydroxycorticoids were 5 mg. per twenty-four hours. An electrocardiogram showed a sinus rhythm with a rate of 63, a P-R interval of 0.15 second, a QRS duration of 0.06 second and a QT interval of 0.44 second. The T waves were uniformly isoelectric or slightly inverted, and prominent U waves were present in all leads. The tracing was consistent with left ventricular hypertrophy and hypokalemia. (Fig. 1.)

Roentgenograms of the chest, abdomen and bones revealed no abnormalities. Intravenous pyelograms and perirenal carbon dioxide insufflation showed no evidence of an adrenal tumor.

An electroencephalogram demonstrated a paroxysmal slow wave activity in the frontal and both central areas, appearing synchronously. The record was consistent with a deep-seated diencephalic focus.

A diagnosis of primary hyperaldosteronism was made.

After an intensive investigation (to be described) and suitable preparation, an exploratory laparotomy was performed on November 4, 1957. Pentothal and cyclopropane were employed as anesthetics. No adrenal tumor could be palpated. The entire right adrenal gland and approximately two-thirds of the left adrenal gland were removed. The remnant was the inferior pole of the left gland and the left adrenal vein leading to the renal vein was left intact.

The right adrenal gland weighed 5 gm., the portion of the left gland weighed 4 gm. The structure appeared normal on gross examination; the cortex seemed slightly thickened in a few places, measuring up to 2 mm. in width. On microscopic examination the two outer zones of the cortex seemed to be thickened in areas but not clearly beyond normal limits. (Fig. 2.) The sections (Pouceau stain) were consistent with that of a normal adrenal gland.

In general the patient made an uneventful clinical recovery. By the end of the second week after operation the blood pressure, taken in the morning before arising, had fallen to 130/70 mm. Hg. However, anorexia and a moderate orthostatic hypotension developed at this time and the blood urea nitrogen rose to 42 mg. per 100 ml. With additional salt in the diet and the passage of time the symptoms of hypotension disappeared and the concentration of blood

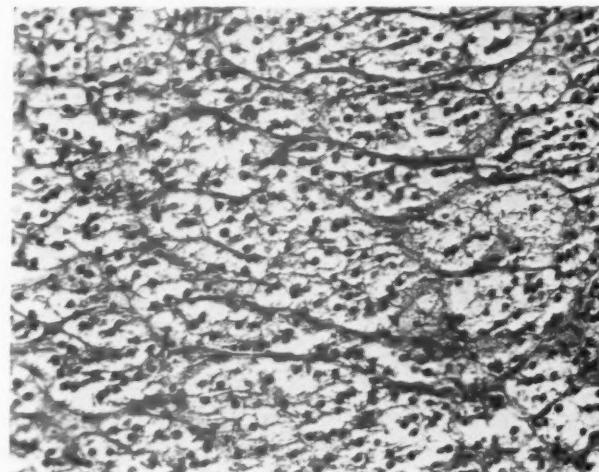


FIG. 2. Microscopic appearance of adrenal cortex.

urea nitrogen decreased to normal. The patient was discharged from the hospital twenty-eight days after the operation, taking no medicine and following a regular diet.

The patient has resumed college work and feels well. The blood pressure, when taken after fifteen minutes of rest, averages 125/85 mm. Hg. During the ten months after operation the patient tolerated an infection of the upper respiratory tract and one episode of acute gastroenteritis without clinical or laboratory evidence of adrenal insufficiency. The blood urea nitrogen, serum sodium, potassium and carbon dioxide concentrations have remained normal.

METHOD OF STUDY

A comprehensive metabolic investigation was performed with dietary control and collection of all urine and stool specimens in the manner described by Reifenstein, Albright and Wells [18]. The investigation was divided into three parts: (1) a control period of twelve days with a dietary potassium of 66 mEq. per day, and sodium of 64 mEq. per day; (2) a twenty-one-day period during which the potassium intake was increased to 300 mEq. per day, the sodium intake remaining unchanged; and (3) a period of twenty-nine days after subtotal adrenalectomy with a dietary potassium of 66 mEq. per day.

The serum sodium and potassium concentrations

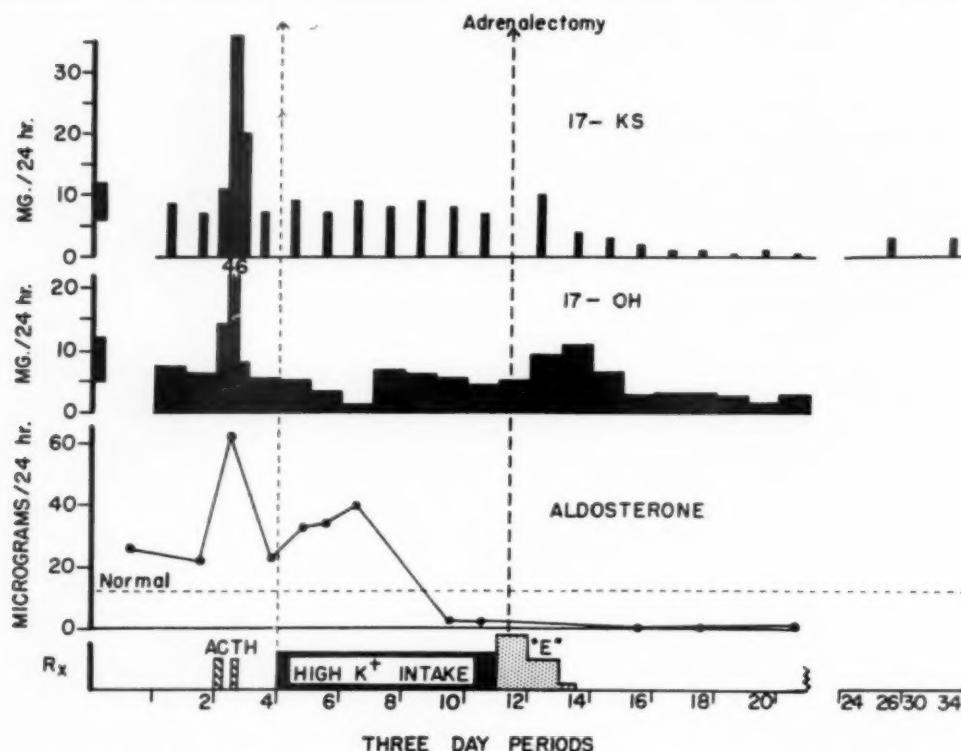


FIG. 3. Alterations in urinary excretion of adrenal steroids during a control period, during increased potassium intake and after subtotal adrenalectomy.

were measured by conventional flame photometry. Carbon dioxide combining power was determined by an electrotitrametric method [79]. Magnesium was determined by a modification of the colorimetric method using titan yellow dye [20].

Urinary 17-ketosteroids were measured by the colorimetric method employing the Zimmermann reaction. Blood samples for the determination of cortisol concentrations in the plasma were analyzed by a modification of Silber and Porter [21], as described by Peterson, Kaner and Guerra [22]. Total 17,21-dihydroxy-20-ketosteroids in the urine were measured by this same procedure following enzymatic hydrolysis with β -glucuronidase as described by Silber and Porter [21].

The urinary aldosterone estimations were made by the following physicochemical method. The twenty-four-hour urine specimens were brought to a pH of 1.5 with concentrated hydrochloric acid, extracted immediately with 0.1 volume of chloroform, and again extracted, after standing twenty-four hours at 25°C., four times with 0.1 volume of chloroform. This procedure released about 90 per cent of the "acid labile" conjugate that would have been released if the hydrolysis had been allowed to continue for ninety-six hours. The chloroform extracts were combined, washed with cold 0.1 normal sodium hydroxide, 0.01 volume two to four times, with cold distilled water, 0.1 volume two times, and brought to dryness in vacuo at 40°C. The residue was then

chromatographed for thirty-six hours in the propylene glycol-toluene system [23]. The region of the chromatogram that included the area of the cortisone standard and 10 cm. below was eluted with 95 per cent ethanol. The sample then was divided into two parts which represent 0.1 and 0.9 of the original urine specimen. These were chromatographed with 0.5, 1, 2, 3, 4 and 4 μ g. standards of cortisol for eight hours in the isoctane-tertiary-butanol-water (E_2B) system [24]. The dry chromatogram was then dipped in a blue tetrazolium-sodium hydroxide solution, heated for twenty-five minutes at 80°C., and examined under ultraviolet light, as described by Neher and Wettstein [25]. The aldosterone was more polar than cortisol, and the visual estimation by blue tetrazolium reduction (BTZ) must equal the visual estimation by soda fluorescence. Under the conditions described, aldosterone was the only substance between the starting line and cortisol standard that demonstrated both BTZ reduction and soda fluorescence. This was not the case when the urine was hydrolyzed with β -glucuronidase. The normal range for this method was from 1 to 10 μ g. per twenty-four hours.

A seven-day urine pool from this patient was processed as described. The aldosterone isolated from this pool was found to have the same potency as authentic aldosterone when bioassayed in adrenalectomized rats. The ultraviolet absorption, sulfuric acid chromagen and the running rate of its diacetate were identical with those of authentic aldosterone.

RESULTS

Aldosterone Excretion. The initial levels of aldosterone were clearly elevated at 22 and 23 µg. per day. (Figs. 3 and 4.) ACTH, 40 mg., was administered intravenously over eight hours on two consecutive days in the third study period. There was a threefold increase in aldosterone excretion to 62 µg. per twenty-four hours on the second day. Four days later this had returned to 23 µg. per twenty-four hours.

In the second phase of this study, one day after the administration of a large dose of potassium, the urine aldosterone rose to 33 µg. per twenty-four hours, and after seven days of large potassium intake it was 40 µg. per day. (Fig. 3.) After fifteen days of intensive potassium therapy the aldosterone had dropped to 2.6 µg. per twenty-four hours, entirely within the normal range. No measurable aldosterone was noted on three determinations in the third phase of study following subtotal adrenalectomy, or two months and six months after the operation. The limit of sensitivity for this method is 0.25 µg. of aldosterone per sample. An ACTH test repeated after six months revealed an insignificant rise to 0.5 µg. per twenty-four hours of aldosterone.

Urinary 17-ketosteroids and 17-hydroxycorticoids. The urinary 17-ketosteroids and 17-hydroxycorticoids were normal initially. Both demonstrated a normal increase in excretion during the ACTH test. During the phase of large potassium intake there was no significant change. There was an increase of both urinary chromagens postoperatively associated with the administration of cortisone. Subsequently the 17-ketosteroids fell to 0.5 mg. per twenty-four hours and later leveled off at 3 mg. per day. The 17-hydroxycorticoids remained low. Six months after operation there was no significant increase in these levels during an ACTH test.

Potassium Balance. During the initial control phase of this investigation the dietary potassium intake was 66 mEq. per day. The serum potassium varied from 2.0 to 2.5 mEq. per L. and the potassium balance was slightly positive. (Fig. 5.) During the administration of ACTH there was no appreciable change in potassium balance. (Fig. 6.) After thirteen days the potassium intake was increased to 300 mEq. per day by the addition of 234 mEq. potassium as potassium chloride in water taken with meals. Except for a three-day period at 200 mEq. potassium per day, the large potassium intake

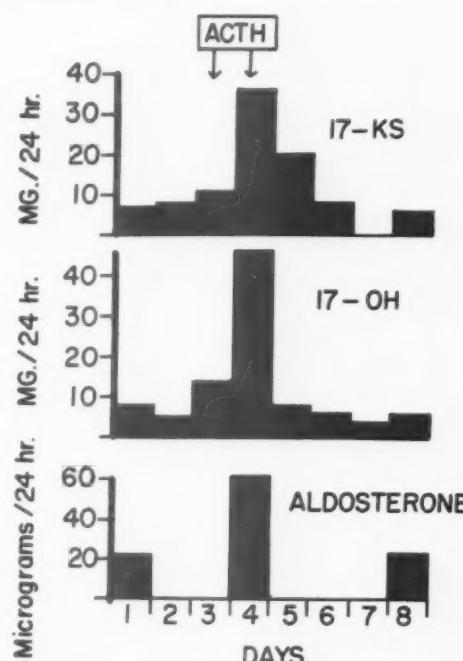


FIG. 4. Changes in urinary steroid excretion in response to an intravenous ACTH test.

was maintained for twenty-one days. There was an increase in the serum potassium to 3.7 mEq. per L. in three days and to 5.7 mEq. per L. by the seventh day. Subsequently the serum potassium remained within normal limits. During the twenty-one days of large potassium intake, the potassium balance became markedly positive and a total of 1,845 mEq. potassium was stored.

Following subtotal adrenalectomy the potassium intake of 66 mEq. was resumed. At this level the potassium balance was in equilibrium and the serum potassium was at the upper limits of normal, higher than prior to surgery. This increase coincided with an increase in the blood urea nitrogen. (Fig. 7.) Subsequently with a decrease in the blood urea nitrogen and on a regular diet at home the serum potassium was 4.5 mEq. per L.

Sodium Balance. During the initial control phase the dietary sodium was 64 mEq. per twenty-four hours. The serum sodium varied from 147 to 151 mEq. per L. and equilibrium of sodium balance was demonstrated. (Fig. 5.) During the administration of ACTH, sodium was retained; and after the administration of ACTH, there was an increase in urinary sodium excretion for two days. (Fig. 6.)

Later during a large potassium intake, there was an abrupt sodium diuresis and a negative sodium balance was present. The serum sodium

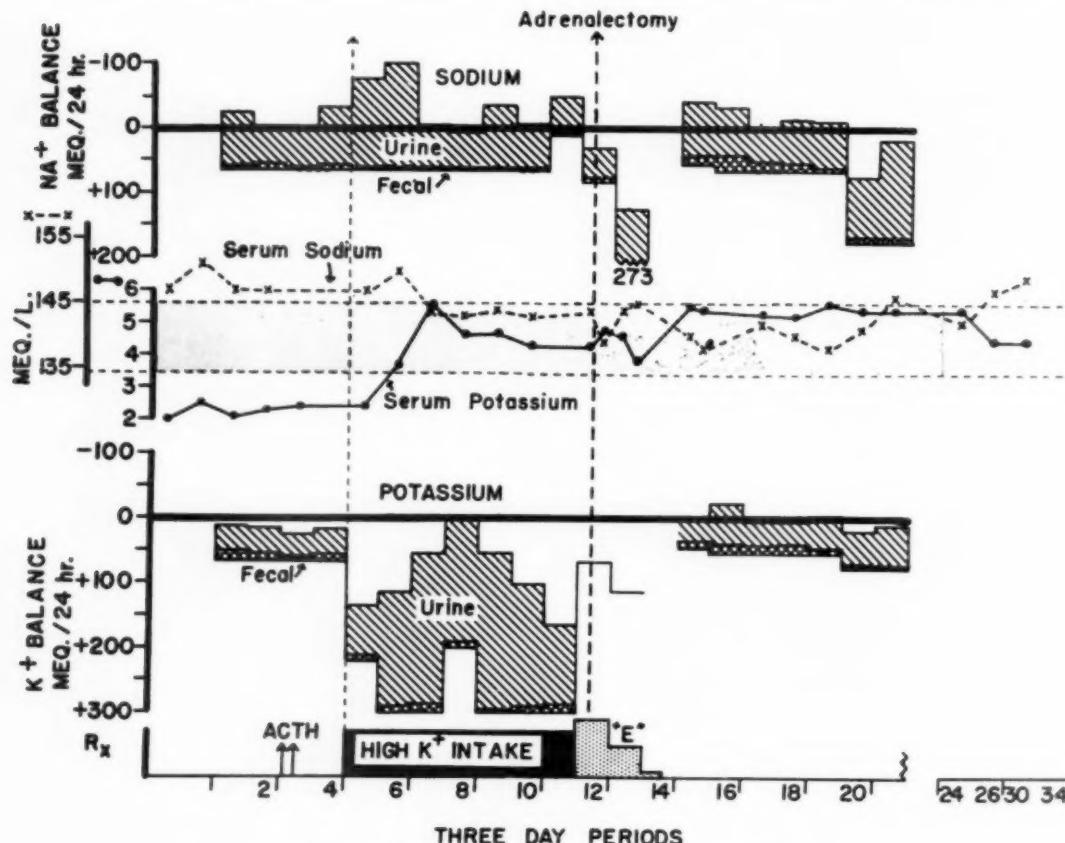


FIG. 5. Sodium and potassium balance study.

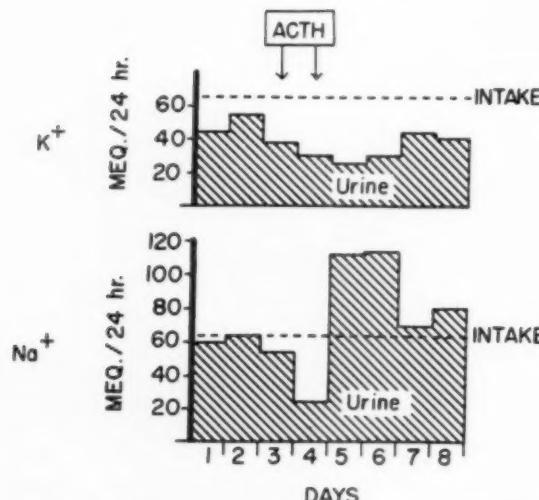


FIG. 6. Effect of intravenous administration of ACTH on the urine electrolytes.

decreased to a constant normal value of 143 mEq. per L. After six days of intensive sodium diuresis, only a small further sodium loss occurred despite continued heavy storage of potassium. During twenty-one days of potassium storage, amounting to 1,845 mEq., there was a loss of 828 mEq. sodium.

In the immediate postoperative period there was marked sodium retention during a large parenteral intake of sodium. Subsequently sodium equilibrium was attained on an intake of 64 mEq. per day. Because of the development of orthostatic hypotension and a rising blood urea nitrogen, the sodium intake was increased to 174 mEq. per day. A positive sodium balance occurred, the blood pressure stabilized at normal levels, and the blood urea nitrogen decreased.

Other Changes During Large Potassium Intake. As the positive potassium balance developed during administration of the large dose of potassium there was a prompt and continuing return to normal of the characteristic disturbances which the patient presented on admission: hypokalemia, elevated carbon dioxide combining power, hypernatremia, hypochloremia and alkaline urine. (Figs. 7 and 8.) The carpal spasms disappeared. There was partial disappearance of the signs of hypokalemia on the electrocardiogram, although these did not disappear completely until after the operation. Although the blood pressure decreased slightly, normal values were reached only after the operation. (Fig. 8.)

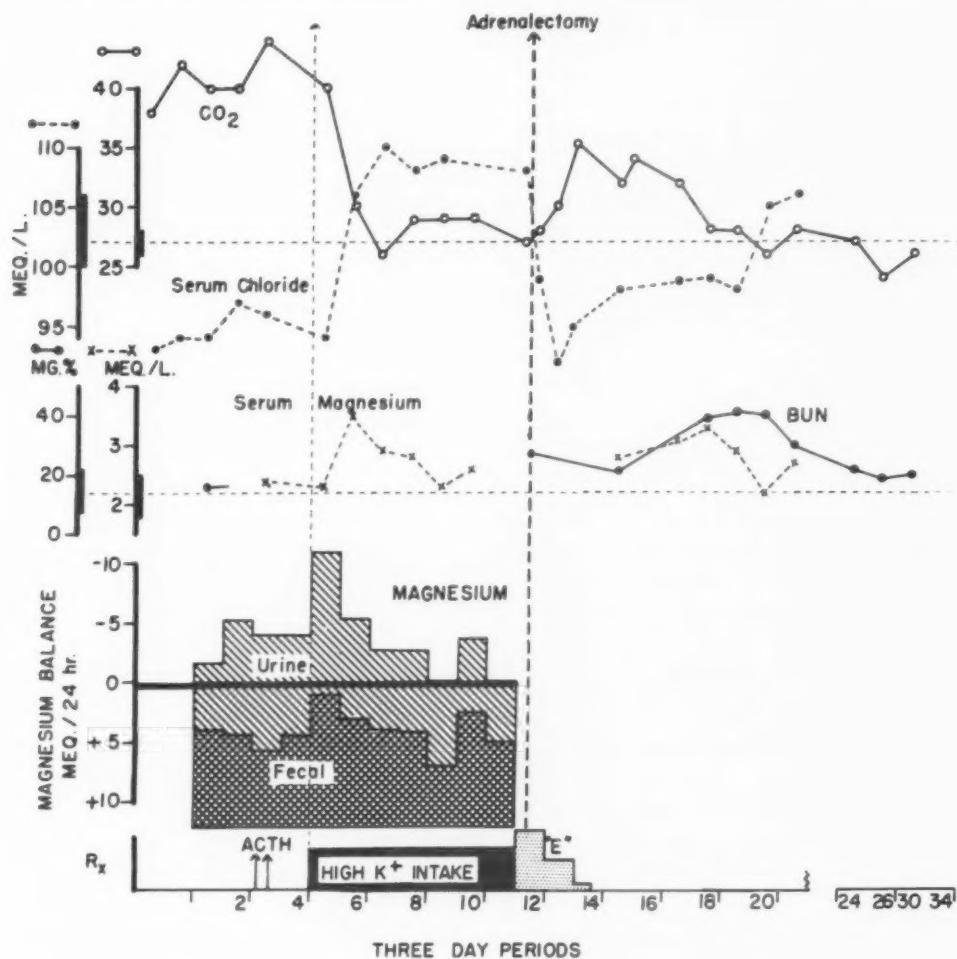


FIG. 7. Serum electrolytes and magnesium balance studies.

Magnesium Balance. A measure of magnesium balance was carried out. (Fig. 7.) The serum magnesium varied from 2.4 to 2.9 mEq. per L. (normal range 1.8 to 2.5 mEq. per L.). One value of 3.5 mEq. per L. occurred after potassium therapy was begun. It appeared that a negative magnesium balance was present in the control phase of study. During the first three-day period of potassium therapy an increase in negative balance occurred. Subsequently magnesium balance was in equilibrium. Unfortunately a laboratory accident resulted in the loss of the postoperative stool specimens for magnesium values and the balance could not be determined. However, in period 21 the magnesium balance was +2 mEq. per twenty-four hours, suggesting that a positive magnesium balance was in process.

Calcium and Phosphorus. The serum calcium and phosphorus remained normal except for an increase in serum phosphorus to 6.3 mg. per cent

when the blood urea nitrogen was elevated. A negative phosphorus balance of 300 to 390 mg. per day was present during the control study phase. Phosphorus equilibrium was attained during the period of potassium therapy. A calcium balance study was not performed.

Electroencephalogram. An electroencephalogram performed during the control study phase was abnormal. Paroxysmal slow wave activity in the frontal and both central areas appeared synchronously. The record was interpreted as compatible with a deep-seated diencephalic focus. Sixteen days postoperatively a repeat electroencephalogram revealed a moderate to marked abnormality. There was a focal abnormality in the right central area. This electroencephalogram appeared more abnormal than the initial recording. Seven months postoperatively there was moderate abnormality, accentuated by hyperventilation. The record was less abnormal and no focal findings were evident.

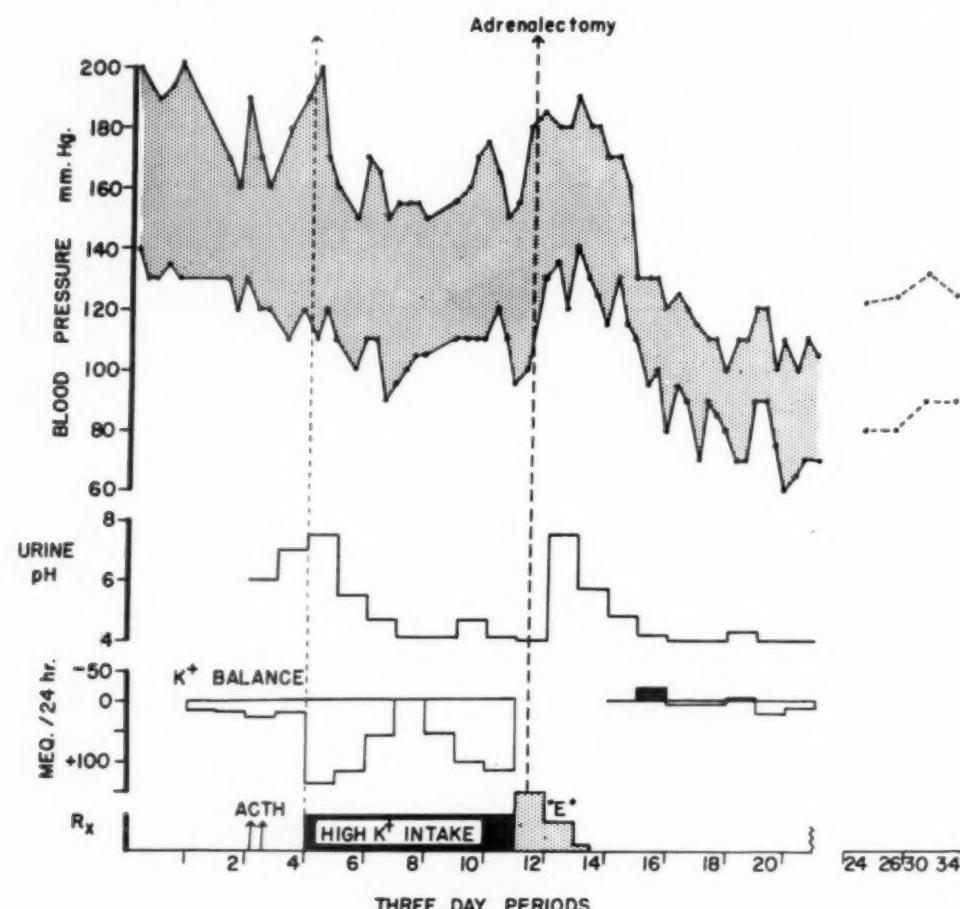


FIG. 8. Alterations in blood pressure and urinary pH during the three phases of study.

COMMENTS

Nature of the Disease. More than twenty cases of hyperaldosteronism have been reported in sufficient detail to allow tabulation of the important findings. If the patients described are listed according to age and the nature of the adrenal lesion, as in the accompanying table (Table I), a clear-cut difference in age distribu-

tion is apparent; seventeen patients with adenomas were all over twenty-seven years old at the time of diagnosis and females predominated. One case of hyperaldosteronism due to carcinoma in a fifty-three year old man has been reported and we have such a case in a thirty-eight year old woman [12,16]. In contrast, in the three reported cases of hyperaldosteronism in the absence of adrenal tumor (normal or

TABLE I
REPORTED DATA OF PATIENTS WITH HYPERALDOSTERONISM (TWENTY-THREE PATIENTS)

Adrenal Pathology	No. of Patients	Age (yr.)	Sex		Initial Serum Concentration (mEq./L.)		
			Male	Female	Potassium	Carbon Dioxide	Sodium
Adenoma.....	17	27-63	4	13	1.4-2.6	23-43	143-156
Carcinoma.....	2	38-53	1	1	1.8-2.1	35-53	150
Hyperplasia.....	4	13-18	2	2	1.7-2.0	32-54	125-151

hyperplastic glands) all the patients were less than eighteen years of age at the time of diagnosis [13-15].

The patient described herein clearly matches this latter group in many ways, although she lacked the evidence of severe or malignant hypertension shown by the cases of Holten and Petersen, and Van Buchem. The long duration of symptoms suggests that in these young patients the specific adrenal hyperfunction in relation to aldosterone may possibly represent a special form of congenital adrenal "hyperplasia." (The word is placed in quotation marks since it is difficult from the findings in this patient, or from reported results, to establish that the adrenal cortex is actually increased in mass.)

There seems no reason to consider the present case as one of salt-losing nephritis with secondary aldosteronism. Bartter [15] suggested the possibility of difficulty in differentiating the two conditions unless it can be shown that urinary sodium falls nearly to zero on sodium restriction, a response which he considers indicative of primary hyperaldosteronism. On a moderate sodium intake (66 mEq.) our patient did not show a negative sodium balance. It may be added that in the experience of Thorn [26], salt-losing nephritis does not simulate hyperaldosteronism.

Preparation for Surgery. During the period of potassium loading most of the clinical and chemical evidence of potassium deficiency disappeared, and the patient stored a large amount of that cation. The importance of this in preparing the patient for surgery was emphasized by our early experience in which a woman with hyperaldosteronism succumbed within forty-eight hours after removal of an adrenal adenoma; the clinical course was complicated, but it appeared likely that inadequate replacement may have played a role in the death. In a number of the cases reported, the patient apparently has also been subjected to surgery without vigorous efforts at potassium replacement. This is obviously unwise, both because of the increased risk of cardiac accidents and of untoward responses to anesthetics in the presence of potassium depletion. The potentiation of the action of curare-like drugs is a particular hazard in this regard. Our present case illustrates the relative ease with which potassium can be replaced, temporarily at least. Milne, Muehrcke and Aird [8] had a similar experience.

Response to Corticotropin. Of special interest

was the increase in urinary aldosterone excretion during the administration of ACTH. The sodium retention during and sodium diuresis after ACTH therapy is suggestive of an increase in aldosterone production, provided that aldosterone is the only adrenal steroid concerned with the renal disposition of sodium, which is very unlikely. This effect is the opposite of that seen by Conn [5] in his original patient (with an adenoma), in whom the administration of ACTH caused prompt sodium diuresis.

If hyperaldosteronism due to hyperplasia in young persons is an entity, some sort of mechanism may eventually be revealed. Present knowledge of the pathways by which aldosterone is synthesized by the adrenal gland is incomplete. One may not postulate an enzymatic block such as is found in congenital adrenal hyperplasia because no deficiency of a known steroid end product exists, and because aldosterone itself is an end product, not an intermediate that could build up if a block existed in the step just beyond it. However, it must be recognized that a shunt of only a few hundred micrograms per day, which might go undetected by present methods, would produce profound changes due to the potency of aldosterone. A more likely explanation would concern extra-adrenal stimuli of aldosterone secretion [27]. The work of Farrell [28] is quite interesting in this respect. He has found that a potent stimulus to aldosterone secretion in dogs is a decrease in intravascular volume and that this response is mediated by changes in tension upon the wall of the right auricle of the heart. This stimulus may be carried by the vagus nerve to a center in the posterior diencephalon that may release a neurohormone which he has called glomerulosotrophic hormone (GTH). This substance apparently can selectively stimulate aldosterone secretion. One indication of cerebral abnormality was presented in our patient by the initial abnormal electroencephalogram which indicated a lesion in the diencephalon. To be sure, encephalographic changes have been noted in a number of states of altered adrenal function.

Response to Potassium. Potassium loading in itself will increase the urinary excretion of aldosterone and hypokalemia will depress the excretion of aldosterone [29]. Laragh and Stoerk [30] demonstrated a rise in urinary excretion of aldosterone by loading dogs with potassium, after prior sodium depletion. These authors suggested that the direct stimulus was the rise in

serum potassium concentration. Moran et al. [31] found a twofold increase in the adrenal output of aldosterone in dogs following a 2 mEq. per L. rise in serum potassium concentration without concomitant changes in serum sodium or intravascular volume. With potassium loading in this case there was an initial rise in the urinary excretion of the acid-labile conjugate aldosterone. This correlated with the rise in serum potassium concentration from 2.5 to 5.7 mEq. per L. Following this the serum potassium fell somewhat and the urinary aldosterone fell to 2 µg. per twenty-four hours. Muller [29] has described a similar biphasic course of aldosterone secretion in a patient with hypokalemia. The observations in this patient might be taken as evidence for a relationship between aldosterone excretion and changes in serum potassium concentration rather than potassium intake or net potassium balance.

SUMMARY

An eighteen year old girl had clinical and laboratory evidence of hyperaldosteronism without an adrenal tumor or obvious adrenal hyperplasia. It is suggested this represents a distinctive form of congenital adrenal hyperfunction. The administration of ACTH led to increased aldosterone excretion and simultaneous sodium retention. Subtotal adrenalectomy after pre-operative preparation with potassium resulted in correction of the abnormalities.

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Sheehan's Syndrome with Diabetes Insipidus*

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POSTPARTUM necrosis of the anterior lobe of the pituitary gland is the most frequent cause of Simmonds' disease [1-3]. Sheehan [3-8] demonstrated that this necrosis occurs frequently in women who die during the puerperium. He correlated necrosis of the anterior lobe of the pituitary gland with severe postpartum hemorrhage and "collapse," and proved the cause to be thrombosis of the sinuses in, and ischemic infarction of, the anterior lobe of the pituitary gland [4]. Sheehan [7] also described the symptoms, signs, and some of the biochemical abnormalities resulting from the hormonal insufficiency produced by this ischemic infarction. Subsequently the sequence of postpartum hemorrhage followed by anterior pituitary insufficiency was entitled Sheehan's syndrome.

The combination of Sheehan's syndrome and diabetes insipidus was first reported by Spain and Geoghegan [9]. The two cases reported by these authors had areas of degeneration in the posterior lobe, as well as necrosis in the anterior lobe, of the pituitary gland. Subsequently other cases have been reported [10-13].

In the cases previously reported [9-13], the diagnosis of diabetes insipidus was based on the presence of polydipsia, polyuria and a low specific gravity of the urine. Definitive tests, i.e., the response of the posterior lobe of the pituitary to the administration of nicotine [14-20] and to the intravenous administration of hypertonic saline solution [19-22], to substantiate the diagnosis of diabetes insipidus were not made. These tests, performed on the patient in the present case report, proved the existence of diabetes insipidus with Sheehan's syndrome.

CASE REPORT

Mrs. R. L. L., a thirty-three year old, white woman, was admitted to St. Michael's Hospital, Grand Forks, North Dakota, on July 5, 1958. The complaint on entry was pain in the chest of two hours' duration on the evening of admission. During the preceding one and a half months, her symptoms

included paroxysmal, productive cough; thoracic backache; headache; fever; and syncopal and near-syncopal episodes. One week preceding admission, a diagnosis of pneumonitis was confirmed by a roentgenogram of the chest. Therapy consisted of tetracycline given orally and an expectorant containing codeine.

The patient reported a progressive weight loss, from 115 pounds before pregnancy to 88 pounds, following the birth of her eighth and last child eight months previously. The delivery was complicated by a severe postpartum hemorrhage. In 1950 the first of nine pregnancies had ended in a spontaneous abortion. Because of placenta praevia, the third delivery was by cesarean section. The next five births were by elective cesarean section. At the time of the fifth cesarean section, her uterus was found to be exceedingly thin. At the time of the sixth and final cesarean section an elective subtotal hysterectomy (and left salpingo-oophorectomy) was performed to prevent future pregnancies with the threat of disastrous rupture of the uterus.

Five hours postpartum, another laparotomy was necessary because of evident intra-abdominal bleeding with associated peripheral circulatory collapse. The abdominal cavity was "full of blood, bleeding from all areas even omentum." Before, during, and subsequent to this procedure, the patient received 7,000 ml. of whole blood, 500 ml. of plasma and 2.6 gm. of fibrinogen plus other intravenous fluids and levarterenol bitartrate to combat the continued blood loss and peripheral circulatory failure.

The patient's postoperative course was complicated for three months by recurring fever (with temperature variations of 3 to 5°F. each day), anorexia, nausea, vomiting, abdominal distention and diarrhea. Repeated episodes of pneumonitis further complicated the picture. An abdominopelvic mass was noted during the puerperium. Treatment consisted of diathermy to the pelvis and administration of antibiotic drugs. During the next seven months, the mass decreased from 12 to 6 cm. in diameter. The exact nature of this mass was not determined. A urine specimen obtained ten days postoperatively, when the patient was no longer receiving parenteral fluids, had a specific gravity of 1.000. Six months postoperatively, the leukocyte count was 7,000 per cu. mm.; the differ-

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tial leukocyte count was 74 per cent lymphocytes, 24 per cent neutrophils, 1 per cent eosinophils, and 1 per cent monocytes.

Subsequent to this eighth and last delivery, the patient failed to lactate for the first time in a postpartum period. During the next ten months pubic hair scarcely regrew, axillary hair became sparse, and skin color remained pale. Excessive tiredness, easy fatigability, cold intolerance, sparsity of scalp hair, and definite loss of libido were also noted. This patient also developed an insatiable thirst with an estimated ingestion of more than 4,000 ml. of water daily and associated polyuria.

The remainder of the history was significant only in that the patient had had a right salpingo-oophorectomy in 1949. The right ovary contained a luteal cyst and several follicular cysts.

Physical examination revealed an emaciated white woman. The temperature was 98.0°F.; pulse, 80 per minute; respirations, 16 per minute; weight, 89 pounds; height, 58½ inches; and blood pressure, 96/56 mm. Hg. The skin was pale, smooth and thin. Scalp hair was somewhat coarse and quite sparse. Axillary hair was diminished, and pubic hair was short and thin. Lymph nodes in the left posterior cervical area and in both inguinal areas were slightly enlarged. At the bases of both lungs, subcrepitant inspiratory rales were audible. Attached to the uterine cervix and anterior to it was a non-tender, irregular, mobile, firm mass 6 cm. in diameter. Pelvic examination was otherwise within normal limits.

The return phase of the tendon reflexes was minimally but definitely slowed. Signs of dehydration or hyperpigmentation of the skin or mucous membranes were not present.

Laboratory data revealed a hemoglobin of 12.4 gm. per cent; hematocrit, 38 per cent; leukocyte count, 5,500 per cu. mm.; differential leukocyte count: 57 per cent lymphocytes, 46 per cent neutrophils, 2 per cent eosinophils, and 2 per cent monocytes. Chest roentgenogram demonstrated resolution of the pneumonitis noted one week earlier. A roentgenogram of the skull revealed no abnormalities. Fasting blood (true) sugar was 72 mg. per cent; and basal metabolic rate, -18 per cent. Serum sodium was 156 mEq./L.; serum potassium, 5.6 mEq./L. See Table I for 17-ketosteroid and 11-oxycorticoid values.

Therapy of the pneumonitis consisted of

TABLE I
RESPONSE OF THE ADRENAL GLANDS TO
ADRENOCORTICOTROPHIC HORMONE
ADMINISTERED INTRAMUSCULARLY

Date (1958)	ACTHAR Gel Intra- muscularly (U.S.P. units)	24-Hour Excretion		
		17-Keto- steroids* (mg.)	11-Oxy- corticoids† (mg.)	Urine (ml.)
7/7	..	1.9	0.94	2,650
7/8	80
7/9	40
7/10	40	2.4	2.7	4,250

* Method of Zimmermann [32]. Normal: 5-15 mg./24 hours.

† Method of Cope and Bain [33]. Normal: 2-6 mg./24 hours.

tetracycline given orally and an expectorant cough mixture. Progress was uneventful; the patient was given ACTHAR® Gel intramuscularly as a therapeutic test for adrenocorticotrophic hormone insufficiency. Dismissal from the hospital was on July 11, 1958.

On July 25, 1958, therapy with triamcinolone, 2 mg. given every six hours, was begun. Two weeks later the patient weighed 91½ pounds, felt stronger, and was no longer anorexic. She was however, intolerant to cold. On August 12, 1958, therapy with desiccated thyroid, 65 mg. daily, was begun.

Two weeks later the patient no longer felt cold, had more energy, and weighed 100 pounds. Her blood pressure was 130/88 mm. Hg. The scalp hair was of finer texture and becoming less sparse. The daily dose of triamcinolone was reduced to 6 mg., and the daily dose of desiccated thyroid was increased to 96 mg.

On September 9, 1958, the patient reported having hot flushes, which lasted about five minutes, ten or more times each day. The blood pressure was 114/78 mm. Hg. The daily dose of triamcinolone was reduced gradually from 6 mg. to 4 mg. over the next three weeks. However, due to a lack of understanding regarding the tablets, the patient continued to take 4 to 8 mg. of triamcinolone daily—the dose probably had been as much as 12 mg. a day prior to this time.

In preparation for subsequent study and clarification of the patient's endocrine status, thyroid medication was stopped on September 9,

TABLE II
RESPONSE OF THE ADRENAL GLANDS TO ADRENOCORTICOTROPHIC HORMONE ADMINISTERED INTRAVENOUSLY

Date (1958)	Procedure	24-Hour Excretion				
		17-Ketosteroids *	17-Hydroxy† Corticosteroids (mg.)	Urine in ml.	Estrogens‡ (μg.)	Pituitary § Gonadotropin (I.U.)
10/6	Hydrocortisone 100 mg., intravenously in 5% dextrose and 0.85% NaCl
10/8	9.0	4.1	2,500	24	53
10/9	10.3	3.0	2,650
10/10	ACTH 25 U.S.P. units intravenously in 5% glucose in 8 hours
10/11	ACTH 25 U.S.P. units intravenously in 5% glucose in 8 hours	14.6	15.5	3,100
10/12	ACTH 25 U.S.P. units intravenously in 5% glucose in 8 hours	17.6	17.6	3,750
10/13	ACTH 25 U.S.P. units intravenously in 5% glucose in 8 hours	20.6	17.2	3,900
10/14	ACTH 25 U.S.P. units intravenously in 5% glucose in 8 hours	18.2	25.1	3,800
10/15	Test for diabetes insipidus
10/16	14.2	5.5	4,500
10/22	19.9	4.0	3,320
10/30	7.7	2.2	2,340
11/11	11.6	2.0	2,490

* Method of Engel-Zimmerman [34]. Normal: 6.5–17.4 mg./24 hours.

† Method of Silber and Porter [35]. Normal: 3.0–11.0 mg./24 hours.

‡ Method of Kober [36]. Normal: 5–160 mcg./24 hours.

§ Method of Crooke et al. [37]. Normal: 50–250 I.U./24 hours.

1958. On September 30, 1958, increasing tiredness was reported. The body weight was then 105 pounds; blood pressure, 114/70 mm. Hg. Polydipsia and polyuria continued unabated during the entire period subsequent to the last delivery.

The last dose of triamcinolone was given on October 4, 1958. The following day the patient was admitted to St. Michael's Hospital for metabolic studies. That night the patient had fever, chills, nausea and vomiting. The oral temperature was 104.4°F.; blood pressure, 90/60 mm. Hg.; and pulse, 128 per minute. The patient appeared obtunded, and her skin was quite warm and dry. Following the intravenous administration of fluids (5 per cent dextrose in 0.85 per cent saline) containing 100 mg. of hydrocortisone, improvement was quite rapid. Her husband and one daughter had a similar illness the same night. They, however, were only mildly affected.

On October 8, 1958, the investigative proce-

dures were begun. Table II presents the values for 17-ketosteroids and 17-hydroxy-corticosteroids. A Papanicolaou smear of the vaginal secretions demonstrated atrophic epithelial cells, no estrogenic effect. Basal metabolic rate was –21 per cent; fasting blood (true) sugar, 68 mg. per cent. Serum carbon dioxide combining power was 29 mMol./L.; serum chlorides, 110 mEq./L. The responses to stimulation by nicotine, Pitressin,® and hypertonic saline solution (Fig. 1) were diagnostic of diabetes insipidus. Dismissal from the hospital was on October 17, 1958.

Therapy was withheld for the next twenty-six days. During this time the patient complained of just not feeling well, always being tired, fatigability, and morning nausea. The intolerance to cold was not as prominent as in July. Serum total proteins, albumin and globulins were normal, as was the blood urea. Serum cholesterol was 269 mg./100 ml. There was no constriction of the visual fields.

Therapy with hydrocortisone, 10 mg. given

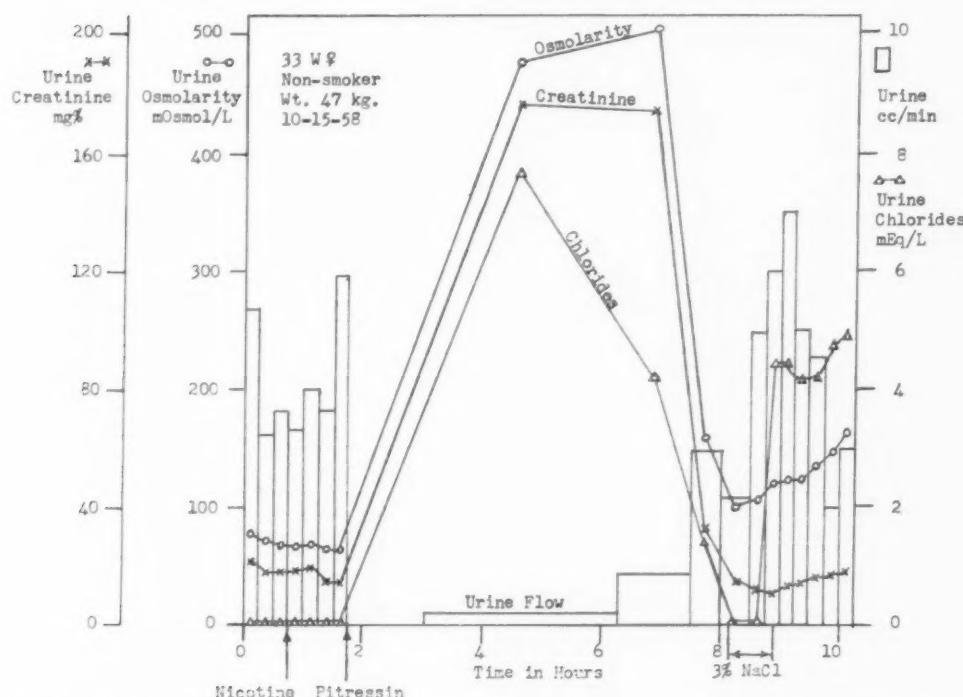


FIG. 1. Test to differentiate psychogenic polydipsia, nephrogenic diabetes insipidus, and diabetes insipidus due to insufficiency of the neurohypophyseal system. The inhalation of the non-filtered smoke from two cigarettes (nicotine) and the intravenous administration of hypertonic saline (10 cc./kg. of body weight/forty-three minutes) both failed, as indicated by the modalities measured, to stimulate the liberation of antidiuretic hormone from the posterior lobe of the pituitary gland. The response to Pitressin (20 units administered intravenously) was normal. These results are diagnostic for insufficiency of the neurohypophyseal system. (Urine osmolarity was determined by the method of Frank et al. [38]; creatinine by the method of Folin and Wu [39]; and chlorides by the method of Schales and Schales [40].

orally every twelve hours, was started on November 12, 1958. Nine days later the patient reported increased energy, stamina and interest in household duties. Thyroid replacement therapy, L-triiodothyronine, 12.5 µg. daily, was begun. The dose of L-triiodothyronine was doubled one week later.

The patient was seen next on December 5, 1958. Morning nausea had ceased. The patient had more stamina and stated that she could not remember when she ever felt better. Blood pressure was 120/86 mm. Hg. Two weeks later, stilbestrol, 1 mg. daily for the first twenty-five days of each month, and testosterone cyclopentylpropionate, 100 mg. intramuscularly at monthly intervals, were added to the therapeutic program.

Polydipsia and polyuria persisted and, according to the patient, had increased. Because of the fear of the frequent hypodermic injections required for the administration of Pitressin tannate and to minimize the cost of drugs, the patient chose to avoid replacement therapy for

the posterior pituitary insufficiency unless it should become necessary. The thirst and frequent urination are no problem except in church.

COMMENTS

Calder [23] and Silver [24] reviewed all the cases of Simmonds' disease reported prior to 1932 and 1933, respectively. In one case reported by Thur [25] of postpartum pituitary insufficiency the patient had polydipsia. This possibly represented the combination of anterior and posterior lobe dysfunction. However, further details were not recorded.

In 1946 Spain and Geoghegan [9] reported two instances of Sheehan's syndrome with diabetes insipidus. Both patients had polydipsia. The first one passed an average of 229 ounces of urine daily during the last four days of her life; death occurred on the tenth postpartum day. The second patient averaged 190 ounces of urine daily for a period of seventy-two hours before becoming incontinent of urine; death occurred eighty-four hours postpartum, twelve

hours after becoming incontinent. At necropsy, both of these patients had lesions in the posterior lobe of the pituitary, as already noted.

Nassar, Djanian and Shanklin's [10] patient had the simultaneous onset of symptoms of anterior pituitary insufficiency, polydipsia and polyuria following a severe postpartum hemorrhage with circulatory collapse. The urine flow diminished in response to the hypodermic injection of Pituitrin.[®] Anterior pituitary insufficiency, as well as posterior pituitary insufficiency, was not documented by physiologic or biochemical studies. Sixteen months postpartum, without becoming pregnant, there was a spontaneous return of menstruation, increase in mammary gland structure, return of the pelvic organs to normal size, and an increase in the blood pressure.

In 1953 Engstrom and Liebman [11] described a twenty-eight-year-old white woman with the onset of anterior pituitary insufficiency following severe postpartum hemorrhage. Six years after this severe hemorrhage, four years after a second pregnancy, the patient had an onset of marked thirst and polyuria. A severe disturbance of the thirst mechanism was demonstrated. Failure to maintain an adequate fluid intake produced hypernatremia and hyperchloremia. The renal tubules responded favorably to the administration of Pitressin. The resulting antidiuresis produced a maximum specific gravity of the urine of only 1.017 (only 1.011 if cortisone was not administered at the same time), decreased the concentrations of serum sodium and chloride to normal, but failed to reduce the polydipsia. This patient's response to tests with hypertonic saline solution or nicotine was not determined.

MacGillivray and Adams' [12] patient had Sheehan's syndrome, polydipsia and polyuria of simultaneous onset. Deprivation of water for five hours resulted in a maximum urinary specific gravity of 1.003. The administration of Pitressin corrected the thirst and the polyuria. Eighteen months postpartum there was a spontaneous recovery of anterior pituitary insufficiency. Menstruation was established, scalp hair grew, and urinary excretion of 17-ketosteroids and corticoids returned to normal.

In 1956 Doxiades and Tiliakos [13] reported a case of Sheehan's syndrome. This patient had the onset of the symptoms of anterior pituitary insufficiency, polydipsia and polyuria four weeks postpartum. The polydipsia and polyuria ceased spontaneously three years after onset.

The authors [13] first saw this patient five years after the onset of the anterior pituitary insufficiency and therefore could not evaluate even the polydipsia and polyuria. Doxiades and Tiliakos [13] stated that postpartum hypopituitarism with diabetes insipidus is extremely rare. However, these authors [13] refer to six cases [26-31] that were not included in the previous discussion.

There can be no doubt that the patient described herein has both Sheehan's syndrome and diabetes insipidus. Since the posterior, as well as the anterior, pituitary insufficiency occurred simultaneously, both can be attributed to the same cause, i.e., postpartum hemorrhage with circulatory collapse.

SUMMARY

A case of Sheehan's syndrome and diabetes insipidus of simultaneous onset is described. The insufficiency of the posterior lobe of the pituitary is proved by the absence of normal physiologic response to the administration of nicotine and intravenously administered hypertonic saline solution.

The literature concerning postpartum anterior pituitary insufficiency associated with posterior pituitary insufficiency is reviewed.

Acknowledgment: I wish to express my appreciation to Mrs. Myra Janke Rada, Department of Biochemistry, University of North Dakota School of Medicine, for the many chemical determinations that made this report possible.

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Intrahepatic Cholestasis Following Administration of Chlorpropamide*

Report of a Case with Electron Microscopic Observations

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CHLOPROPAMIDE (P-607, Diabinese[®]), like tolbutamide [7] an arylsulfonylurea derivative, is a new oral hypoglycemic agent recently introduced into clinical practice [2-9]. The present report describes the occurrence of intrahepatic cholestasis, simulating extrahepatic biliary obstruction, following use of this drug.

Chlorpropamide (1-[p-chlorobenzenesulfonyl]-3-propylurea) differs from tolbutamide in that a chloride ion replaces the methyl group in the para position, and the side chain includes a propyl rather than a butyl group. The drug is slowly excreted in the urine [10].

The production of intrahepatic cholestasis with biliary tract obstruction by the administration of drugs has been noted frequently in recent years [11]. The drugs implicated include arsphenamine [12], methyltestosterone [13,14], methimazole [15], thiouracil [16], para-aminobenzyl caffeine hydrochloride [17], dinitrophenol [12], cinchophen [11], sulfadiazine [18], para-aminosalicylic acid [19], norethandrolone (Nilevar[®]) [20,21], and very prominently, chlorpromazine [22-28]. More recent reports associate cholestasis with promazine, mepazine (Pacatal[®]) [29], chlorothiazide [30], ectylurea (Nostyn[®]) [31], Carbarsone[®] [32] and prochlorperazine (Compazine[®]) [33].

The clinical picture is one of obstructive jaundice, with laboratory findings of increased serum alkaline phosphatase and total cholesterol. Evidence of hepatocellular damage does occur, as indicated particularly by early serum glutamic oxaloacetic transaminase elevations and bromsulphalein retention, but may be minimal, transient, and not noted in routine diagnostic studies [34,35]. Such findings have been demon-

strated particularly in the investigation of intrahepatic cholestasis due to norethandrolone [21,36]. Pathologically, the essential feature is increased stasis of bile, most marked in the centrolobular area, with bile pigment in liver and Kupffer cells, and bile thrombi in canaliculi [23,27]. Periportal and periductular cellular infiltration, at times eosinophilic, is variable in occurrence. It is typically absent in cholestasis associated with methyltestosterone, norethandrolone, para-aminobenzyl caffeine hydrochloride, methimazole and sulfadiazine [37]. There may be minimal cellular changes, some of these secondary to bile stasis; feathery degeneration and multinucleated cells are seen. This picture is typical of intrahepatic cholestasis but may also be found in cases of extrahepatic biliary tract obstruction. However, the presence of hydrohepatosis, manifested by dilated bile ducts, bile extravasation and bile infarcts, is pathognomonic of obstruction of the extrahepatic biliary tract [38].

Hepatotoxicity has been previously reported in association with the administration of chlorpropamide. In a series of 1,819 cases collected from the literature, fourteen cases of damage to the liver have been noted [39-46]. There is evidence from the material available that in nine patients a picture of intrahepatic cholestasis developed, giving a total incidence of 0.5 per cent [39,40,42,44-46]. Inasmuch as chlorpropamide is increasingly used in the management of diabetes, the importance of calling attention to this manifestation, to prevent surgical exploration for extrahepatic biliary tract obstruction, is obvious.

Other reported side effects have been nausea,

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TABLE I
RESULTS OF HEPATIC TESTS DURING COURSE OF JAUNDICE AND AFTER CHALLENGE DOSES OF
TOLBUTAMIDE AND CHLORPROPAMIDE

Date (1959)	Serum				Urine Bile	Urine Urobilinogen	Serum Albumin Globulin (gm. %)	Cephalin Floccula- tion	Thymol Turbidity (units)
	Total Bilirubin (mg. %)	Alkaline Phosphatase (K.-A. units)	Total Cholesterol (mg. %)	SGO-T (units)					
January	5 30	26.2	4 plus	1:2	3.4/4.0	1.9
	7 ...	23.5
	8 24	21	635	91	2 plus	1:40	0	...
	14 19.2	22.2	1 plus	1:20	2.9/3.5
	16 19.4	21.9	560	...	2 plus	1:40	0	1.3
	23 12.6	...	420	2.6/3.4
	26 13.2	19.8	390	1.7
	February 2	9.2	19.0	420	86
	9 6.6	17	400
	10 	130	0	1:80
March	17 3.5	14	320	68
	26 2.3	11.5	310	86
	28 	2 plus	...
	March 2	2.4	12.5	274	3.6/3.3	1.3
April	9 1.3	9.6	...	70
	16 	31
	24 0.6	41	0	...
Tolbutamide on 3/28, 3/29									
March 30	0.8	9.7	224
April 1	0.7	10.3	236
Chlorpropamide on 4/2 to 4/5									
4	0.7	10.4	...	69
7	0.7	10.2	...	60	0	1:10

anorexia, dizziness, dermatitis, albuminuria, leukopenia and thrombocytopenia. Many toxic reactions have occurred at high dosage levels, exceeding 1 gm. per day, with subsidence on reduction or cessation of therapy [5,47].

CASE REPORT

D. J., a sixty-seven year old white housewife, was admitted to The Mount Sinai Hospital for the first time on January 3, 1959, with the chief complaint of itching of two weeks' duration. The patient had had diabetes mellitus for seventeen years, most recently treated with 35 units of NPH insulin daily. Urine specimens tested at home showed 1-2 plus glycosuria. In August 1958 the patient had nausea, vomiting, arthritic pains and depression, and was given 2-hydroxy-2-phenyl-ethyl carbamate (Sinaxar®) in Sep-

tember. In October, because of persistence of symptoms, administration of methocarbamol (Robaxin®) was started, and Sinaxar was discontinued. The daily insulin requirements at this time were 50 units Lente, 20 units regular. On October 24, 1958, administration of phenylbutazone was started and Robaxin was discontinued. On October 31 therapy with chlorpropamide (Diabinese®), 0.25 gm. twice a day, was begun, and continued until November 28 when the patient had symptoms of weakness and vomiting. At this time digitoxin was prescribed for atrial fibrillation. Two weeks prior to admission (about December 15, 1958) pruritus was noted, with dark urine, nausea, malaise, anorexia and clay-colored stools.

No history of intolerance to fatty food, exposure to hepatitis, virus, ingestion of iproniazid, chlorpromazine or other hepatotoxins was elicited. There were no past blood transfusions or history of disease of the

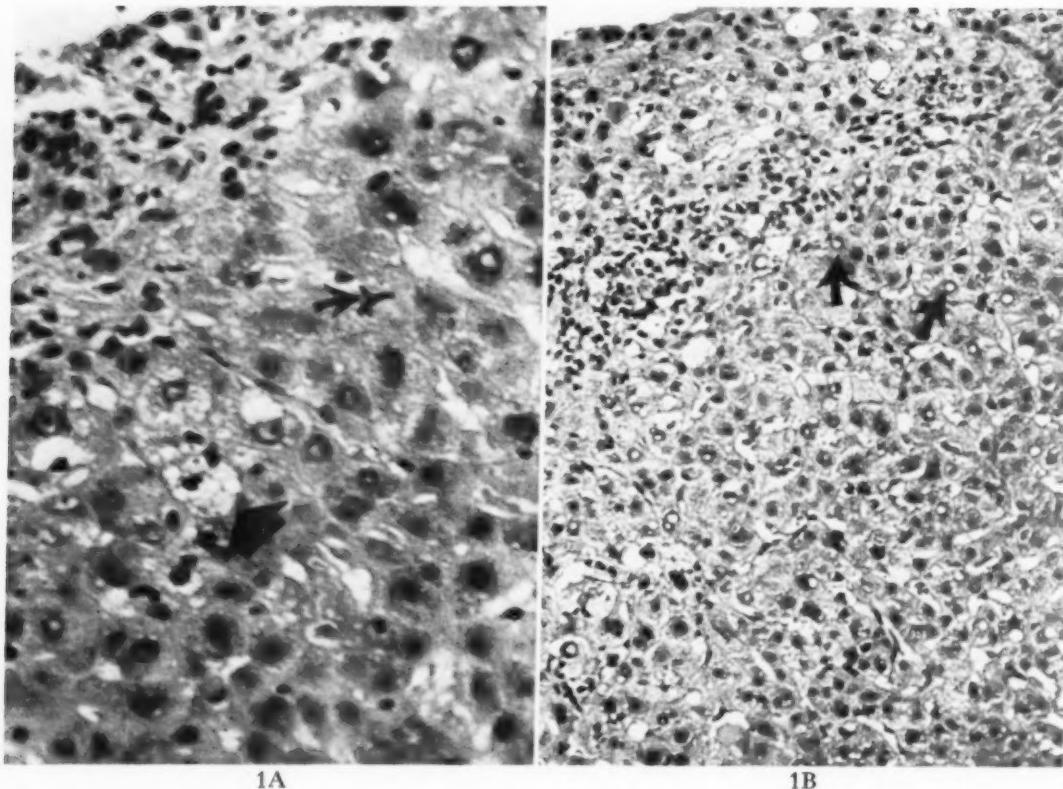


FIG. 1. A, biopsy specimen of liver showing bile thrombus (small arrow) and liver cell undergoing feathery degeneration. Hematoxylin and eosin. Original magnification $\times 240$. B, inflammatory cellular infiltration of portal tract, increased number and size of Kupffer cells and numerous glycogen-filled nuclei in lobular periphery (arrows). Hematoxylin and eosin. Original magnification $\times 63$.



FIG. 2. Electron micrograph of two hepatic cell mitochondria with inclusion arranged as a cluster of short parallel lines (small arrow) or long parallel bars (large arrow). Original magnification $\times 120,000$.

gallbladder. The review of systems was non-contributory. Intermittent claudication was recently noted. The patient had undergone tonsillectomy ten years before. There were no pregnancies. Postmenopausal bleeding was absent.

The patient was born in Hungary, smoked moderately, took no alcohol, and ate a balanced diet.

The patient was a well developed, icteric, lethargic and irritable white woman. Physical examination disclosed a blood pressure of 130/70 mm. Hg; pulse, 88 per minute; respirations, 14 per minute; temperature, 99.6°F. Xanthelasma were absent. The fundi showed arteriolar narrowing, bilateral pinpoint and flame hemorrhages, yellow exudates and microaneurysms. The patient was edentulous. The antero-posterior thoracic diameter was increased, with diminished breath sounds at the bases. The heart was enlarged to the left, the rhythm was regular with occasional premature contractions. A grade 3 holosystolic decrescendo murmur was heard at the apex and precordium. The liver was palpated 1 cm. below the right costal margin; the edge was smooth and mild shock tenderness was present in the right upper quadrant. The spleen was not felt and no abdominal wall tenderness, guarding or rebound was elicited. No pulses were palpable below the femorals.

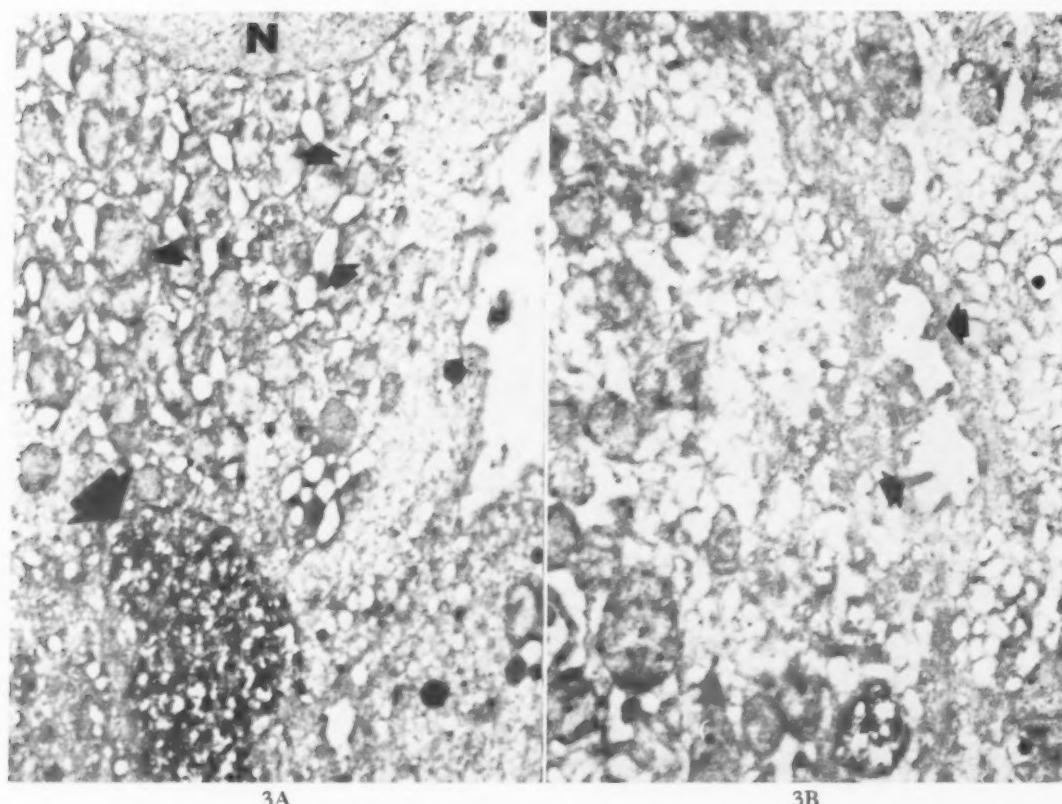


FIG. 3. A, electron micrograph showing disrupted and cystic endoplasmic reticulum (small arrows) and dilated bile canalculus filled with dense material, presumably bile (large arrow). The nucleus is labeled N. Original magnification $\times 10,000$. B, undilated bile canalculus with shortened and irregular microvilli (arrows) which are fewer in number than normal. Original magnification $\times 32,000$.

The ankle jerks were absent. The skin was icteric, and excoriated papules were seen on the neck, chest and arm. Soft lymph nodes, 1 cm. in diameter, were felt in both axillas. Rectal examination revealed no masses.

The laboratory data were as follows: hemoglobin, 14 gm. per cent; white blood cell count, 9,850 per cu. mm., with a differential of 71 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes, 2 per cent eosinophils and 4 per cent monocytes. Platelets were normal. Urine analysis showed: acid reaction; specific gravity, 1.018 to 1.020; albumin, negative to faint trace; sugar, negative to 4 plus; acetone, negative; and 4 to 5 white blood cells per high power field. The erythrocyte sedimentation rate (Westergren) on January 5 was 85 mm. in the first hour, and on February 25 was 20 mm. The stool was grey on admission; subsequently it was normal, without occult blood. The blood urea nitrogen was 16 mg. per cent. The fasting blood sugar was 68 to 216 mg. per cent. The serum electrolytes and serum amylase were within normal limits. The results of hepatic tests are summarized in Table I.

The venous pressure was 105 mm.; circulation time and electrocardiogram were within normal limits. Coagulation time, bleeding time, Rumpel-Leeds test and clot retraction were normal. The prothrombin time on admission was 16 seconds (control, 13.5

seconds) and subsequently 13.5 seconds (control, 13 seconds). The serum iron was 183 μg . per cent; the total iron binding capacity was 342 μg . per cent. The serum free B_{12} was 100 μg . per ml., total B_{12} was 680 μg . per ml.

On January 19 serum lipid partition showed cholesterol, 378 mg. per cent; esters, 103 mg. per cent; and phospholipids, 676 mg. per cent. Serum globulin fractional analysis revealed a low mucoprotein. Serological tests for syphilis were negative. L.E. preparations were negative, as was the latex fixation test. There was 17 per cent bromsulphalein retention in forty-five minutes, a figure which remained unchanged throughout the hospital stay. Oral cholecystography revealed a normal gallbladder. An upper gastrointestinal roentgenographic series revealed no abnormalities. X-ray examination of the chest showed the heart to be at the upper limit of normal in its transverse diameter. X-ray examination of the parotid regions showed no definite calcifications. Hand and wrist x-ray films revealed osteoarthritis.

The diabetic status was controlled with 50 to 55 units of Lente insulin daily. Bilateral non-tender parotid swelling was noted during the second hospital week.

A biopsy of the liver was performed on January 9, 1959, with a 1.2 mm. Menghini needle using a trans-

thoracic approach. The hepatic architecture was found to be intact. In the lobular parenchyma scattered areas of focal necrosis were apparent. Bile stasis was prominent, especially in the centrolobular zone, with bile thrombi and feathery degeneration of cells. (Fig. 1A.) Fat droplets were scattered throughout, but were most numerous in the central and intermediate zones. Glycogen-filled nuclei were noted frequently near the lobular periphery. The portal tracts were enlarged and infiltrated with inflammatory cells including leukocytes, mononuclear cells and eosinophils. (Fig. 1B.) Ductular proliferation was noted in and around the portal tracts and inflammatory exudate seemed to surround these ductules. Examination of the same tissue in the electron microscope after osmium tetroxide fixation showed the liver cells to be intact. The mitochondria were normal in size and shape but some contained parallel lines or bars of electron-dense material. (Fig. 2.) The endoplasmic reticulum was disrupted and swollen. (Fig. 3A.) The bile canaliculi were either dilated and filled with a dense material, presumably bile, (Fig. 3A) or normal in size but lined by abnormal canaliculi. (Fig. 3B.) Examination of a portal tract showed some extracellular fat, some increase in fibers arranged in irregular bundles, and an increase in lymph vessels. One ductule was seen but its lumen was not clearly apparent, presumably because of the plane of sectioning.

The patient's icterus subsided during her hospitalization. (Table 1.) With bed rest and regulation of her diabetic state, there was concomitant improvement in her general well-being. She was then given two oral doses of 0.5 gm. tolbutamide on successive days. There was no change in the serum bilirubin, alkaline phosphatase or cholesterol. After this challenge, 50 mg. of chlorpropamide was given daily for four successive days. The serum glutamic-oxaloacetic transaminase was noted to have increased to 69 units and 60 units on the second and fifth days after administration was begun. This was interpreted as a significant rise and further chlorpropamide challenge doses were withheld. There was no increase in serum bilirubin, serum alkaline phosphatase or bromsulphalein retention at this time.

COMMENTS

The pathogenesis of intrahepatic cholestasis has been a subject of much investigation and dispute. Etiologically, it may be drug-induced or may represent a possible variant of viral hepatitis, periacinar or cholangiolitic hepatitis [48,49]. Whether the cholestasis following administration of drugs is a toxic or an allergic manifestation is not known. The evidence that this represents a hypersensitivity phenomenon, notably in chlorpromazine jaundice, includes the following points: onset after small dosage,

a definite latent period before onset of cholestasis, other concomitant or independent reactions commonly considered allergic, the presence of periportal and peripheral eosinophilia at times, and accelerated and positive reactions upon challenge, with some suggestion of cross sensitivity [11,28,50]. Those favoring the thesis that intrahepatic cholestasis represents a direct hepatotoxic effect may point to the inconstant results with challenge [14,50] (although one may postulate desensitization [34]), and to the high incidence (20 to 50 per cent) of laboratory evidence of damage to the liver in patients carefully observed under therapy [34,35].

The exact mechanism of cholestasis is obscure, although theories are abundant. A widely held postulate is that of injury to the ductules, producing increased permeability and consequent leakage of bile and water, leading to inspissation of bile and regurgitation jaundice [38,48]. The older concept of "albuminocholie" postulates passage of proteinaceous material into the biliary radicles and consequent precipitation of bile [38,51]. Periportal cellular infiltration has been considered by some to be secondary to cholestasis [37], but others believe that the exudate is primary and toxic, and that secondary compression of ductules occurs [18]. Other investigators invoke a change in composition of bile due to the presence of the drug, with consequent increased viscosity and bile stasis [23]. Changes in composition of bile and viscosity have also been blamed on direct injury to the liver cell [15,21,52,53].

Further insight into the mechanism of intrahepatic cholestasis has been acquired by the electron microscopic finding of altered microvilli in undilated bile canaliculi of the liver cells, an observation made in this patient and others with intrahepatic cholestasis [54]. This alteration appears to be the primary morphological change in intrahepatic cholestasis and probably reflects altered function of this membrane, possibly with formation of abnormal bile-containing protein and polysaccharide and with loss of fluid from the bile. These factors would increase the tendency for precipitation to occur, with formation of bile plugs which focally obstruct bile flow. Increased intracanalicular pressure results, causing rupture of canaliculi into nearby extensions of the perisinusoidal spaces.

Unusual structures may appear in the mitochondria after administration of the sulfonyl-

urea derivative. Similar structures have been seen in patients receiving chlorothiazide, chlorpromazine and sulfisoxazole [55]. The significance of this finding is not known.

In the patient reported, the pathologic findings are inconsistent with infectious hepatitis. The absence of a history of intolerance to fatty food, fever, abdominal pain, tenderness and leukocytosis, as well as the periportal eosinophilic infiltrate noted, argues against the diagnosis of cholestasis with obstruction of the common bile duct. The increase of serum glutamic-oxaloacetic transaminase noted in response to small challenge doses of chlorpropamide would implicate this drug as etiologic in our case. There was no demonstration of cross sensitivity to a close analogue, tolbutamide. The biopsy of the liver was similar to that seen in other drug-induced cholestatic reactions. Of interest is the unexplained parotid gland enlargement which our patient exhibited. Although enlargement of the parotid gland is associated with states of malnutrition, chronic disease of the liver, and rarely in diabetes mellitus, its occurrence in acute intrahepatic cholestasis following administration of drugs has not been noted [56].

SUMMARY

1. A case of intrahepatic cholestasis secondary to the administration of chlorpropamide is presented.

2. Of a series of 1,819 diabetic subjects receiving chlorpropamide, collected from the literature, there were nine cases suggestive of intrahepatic cholestasis.

3. Abnormalities of the microvilli in the bile canaliculi of the liver cells, as seen in the electron microscope, suggest that this is the primary morphologic change in this and other instances of intrahepatic cholestasis. Unusual mitochondrial inclusions were also noted, the nature of which is unknown.

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Lipoid Dermato-Arthritis*

Reticulohistiocytoma of the Skin and Joints

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IN recent years lipoid dermatitis has emerged as a new clinical and pathologic entity. The condition is characterized by severe, often mutilating polyarthritis and by cutaneous papules and nodules. Lipoid-laden giant histiocytes are present in both the skin and synovial tissues. The blood lipid levels may be normal or slightly elevated.

Allen [1] was the first to use the term reticulohistiocytoma for this condition. The disorder has also been called reticulohistiocytosis and reticulohistiocytic granuloma. In view of the disordered lipid metabolism and the involvement of joints in this condition, however, the term lipoid dermatitis is now preferred.

We intend to review the known facts about lipoid dermatitis and to report the results of our investigations of a patient afflicted with this unusual disease.

Clinical Features. Thus far there have been at least twenty recorded cases of lipoid dermatitis, reported mostly by dermatologists. Females have outnumbered males by a ratio of 2 to 1. The average age of onset is forty, with extremes of twenty and sixty-six years. The condition has occurred in the Caucasian, Oriental and Indian races. Lipoid dermatitis is not hereditary.

The onset of the arthritis may precede, accompany, or follow the onset of the cutaneous eruption. The arthritis clinically resembles rheumatoid arthritis. However, any joint may be involved, including the terminal interphalangeal joints of the fingers, the posterior articulations of the lumbar spine and the costotransverse joints. In addition, when the arthritis is progressive there results a deformity of the fingers known as "la main en lorgnette"

(telescopic or opera glass hand). The fingers become shorter due to destruction of the interphalangeal joints and subarticular bone. The skin of the fingers becomes redundant and lies in flabby folds. By varying the tension on the terminal phalanx, the fingers can be elongated or compressed like a telescope or an accordion. There may be hyperextensibility of the interphalangeal joints. Swellings of the tendon-sheath may also occur.

The cutaneous papules and nodules are firm and vary in size from 2 mm. to 2 cm. The lesions vary from a flesh color to a yellowish or reddish brown hue. They are found most commonly on the scalp, face, dorsum of the fingers, forearms and trunk. Some of the nodules resemble xanthomas. Xanthelasmas of the eyelids have been recorded in one-fourth of the patients. Mucosal lesions of the lips and tongue may be present and on one occasion a nodule of the larynx has been observed.

Solitary nodules may occur without associated arthritis [1-3] and some authors consider this is an abortive form of the disease.

Hypo- and hyperthyroidism have each been associated with lipoid dermatitis on one occasion but the majority of patients have had no thyroid or endocrine abnormalities. The liver and spleen are not involved.

X-ray Findings. There may be rapid destruction of all the interphalangeal joints and subarticular bone, resulting in sharp, narrow bony edges and a widening of the articular spaces. These findings differ from rheumatoid arthritis in which the distal interphalangeal joints are not involved and the joint spaces become narrowed as the disease progresses. A diffuse, generalized osteoporosis is often present. However,

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FIG. 1. "La main en lorgnette," the result of extensive destruction of joint cartilage and subarticular bone. The fingers are shortened and the skin lies in redundant folds.

there are no circumscribed, punched-out long bone or skull lesions such as are seen in Hand-Schüller-Christian disease or eosinophilic granuloma of bone.

Pathology. The diagnosis of lipoid dermatitis is made by biopsy of a cutaneous nodule or of synovial tissue from an involved joint. In well developed lesions characteristic multinucleated giant cells (up to 50 microns in diameter) with abundant, eosinophilic, finely granular, non-foamy cytoplasm are found in both the affected skin and synovial tissues. Numerous histiocytes are also present. The giant cells may contain 1 to 15 nuclei scattered throughout the cell. In the skin the giant cells are scattered diffusely throughout the dermis, pushing aside the collagen bundles which separate them. The giant cell infiltration is not encapsulated but is separated from the intact epidermis by a narrow zone of normal collagen. Occasionally a patchy mid-dermal aggregate of lymphocytes is also present. The epidermis may be thinned and the rete ridges flattened by the underlying dermal infiltrate.

Postmortem findings in two cases [4] have revealed a fibrinous pericarditis. The characteristic giant cells were found not only in the skin and synovial tissues but also in the subcutaneous tissues, in bronchial lymph nodes, bone marrow, periosteum and endocardium. The liver and spleen were not involved.

Prognosis. The course of the disease is of interest. Four patients have died but in no case was the cause of death directly related to lipoid dermatitis. Three of the deaths were due to malignancy (sarcoma of the axilla, adenocarcinoma of the stomach, bronchogenic car-

cinoma) and the other to an unexplained short febrile illness.

The course and severity of the arthritis is variable. In the majority of patients severe arthritis develops which becomes stabilized after several years and does not increase in severity. In a few patients the arthritis is progressive and incapacitating but in others the arthritis may improve so that the patients can carry on normal activities. In most patients the cutaneous nodules have eventually regressed or disappeared spontaneously.

Treatment. X-ray therapy, nitrogen mustard, penicillin and low fat diets have all proved valueless. The corticosteroid hormones may cause temporary regression of the cutaneous lesions but they recur when administration of the steroids is stopped. The corticosteroids have been reported to have little effect on the arthritis [4]. We have, however, noted some improvement in joint pain and mobility with the use of triamcinolone.

ILLUSTRATIVE CASE

B. C., a fifty-five year old Negro housewife, was well until the age of forty-nine when painful arthritis developed in the right ankle, left elbow, both knees and both hips. There were no effusions or redness of the joints. Three years later both hands and wrists became painful and she noted a progressive decrease in the length of her fingers. The skin of her fingers became more wrinkled as the digits became shorter. As the arthritis progressed, her hands finally developed the typical appearance of "la main en lorgnette." (Fig. 1.) Her arthritis became increasingly incapacitating and progressed to the point where she could not walk.

At age fifty-two, simultaneously with the spread of the arthritis to her hands, cutaneous papules and nodules developed on her scalp, retroauricular areas, perinasal area, cheeks, trunk, arms and hands. Nodules also developed on her lips and tongue. At the same time typical xanthelasma appeared on her eyelids. The nodules varied in size from 2 mm. to 1.5 cm. On the scalp and retroauricular areas they were of a yellow-brown or flesh color and often coalesced to form elevated, pebbly plaques. (Fig. 2.) In other areas the nodules were smooth, discrete, firm and reddish brown. (Fig. 3.) The nodules of the lips and posterior third of the tongue were the color of the mucous membrane. Some of her cutaneous nodules disappeared spontaneously but others continued to erupt.

There was no family history of arthritis or disease of the skin.

The patient came to our attention in November 1958 when she was hospitalized for a fracture of the



FIG. 2. Numerous nodules of the scalp have coalesced to give a pebbly appearance.

distal third of the right tibia which occurred after a fall. She was afebrile and, except for the fracture and the previously described cutaneous and arthritic changes, her physical examination revealed no abnormalities.

The hemoglobin was 10.6 gm. per cent; serum iron, 61 μ g. per cent. The serum was not turbid. On November 20, 1958 the serum cholesterol was 294 mg. per cent (normal 150 to 250 mg. per cent); total blood lipids, 1,144 mg. per cent (normal 400 to 800 mg. per cent); phospholipids, 272 mg. per cent (normal 220 to 280 mg. per cent); and total fatty acids, 442 mg. per cent (normal 250 to 360 mg. per cent). On January 15, 1959 the total cholesterol was 271 mg. per cent; total lipids, 1,045 mg. per cent; phospholipids, 338 mg. per cent; and fatty acids, 300 mg. per cent. Analysis of the serum lipoproteins by paper electrophoresis [5] on December 8, 1958 revealed 80.1 per cent beta lipoprotein, 10.1 per cent alpha lipoprotein and 9.8 per cent neutral fat (normally beta lipoprotein is 45 to 60 per cent, alpha lipoprotein is 20 to 45 per cent and neutral fat 10 to 20 per cent). The electrophoretic lipoprotein pattern was abnormal, showing increased staining of the beta lipoprotein and migration of the lipoprotein ahead of the beta globulin level toward the alpha 2 globulin level. (Fig. 4.) Electrophoretic analysis of the serum glycoproteins revealed glycoprotein in all fractions, with heaviest concentration in the alpha 1 and alpha 2 fractions. The serum protein electrophoretic pattern was normal. The sedimentation rate was 38 mm. per hour (Wintrobe). On May 1, 1959, the total cholesterol was 360 mg. per cent.

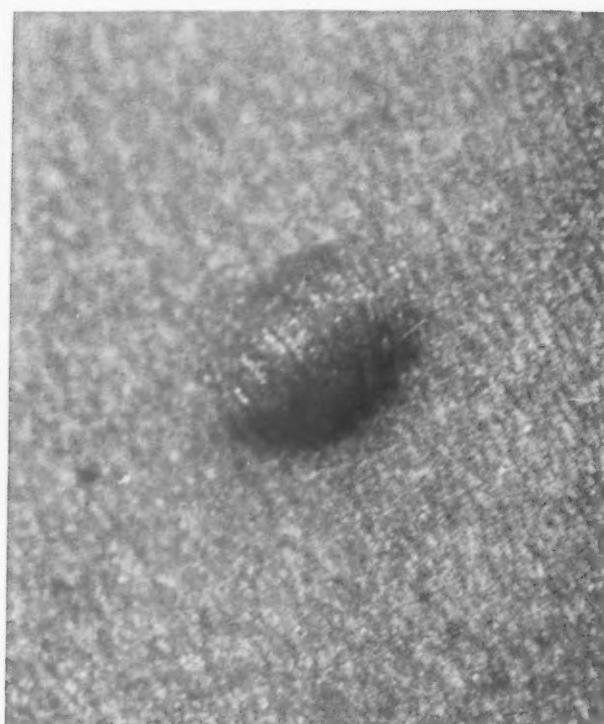


FIG. 3. Discrete reddish brown nodule of the back, resembling a xanthoma.

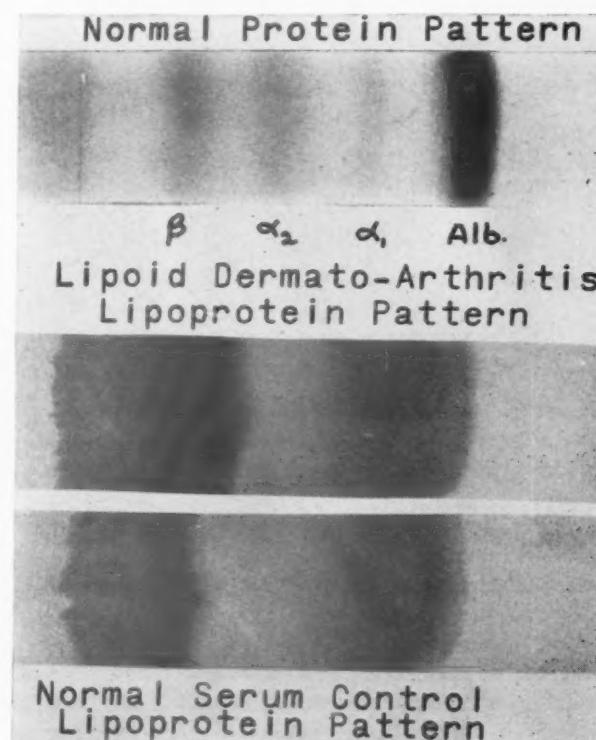


FIG. 4. A normal protein electrophoretic pattern is seen in lipoid dermatitis. However, there is an abnormal lipoprotein pattern. There is more intense staining of the beta lipoprotein when compared to normal serum and a new band appears migrating ahead of the beta lipoprotein toward the alpha-2 globulin level of the protein pattern.



FIG. 5. Roentgenogram of hands and wrists showing extensive joint destruction.



FIG. 6. Roentgenogram of hips showing destruction of hip joints and protrusion of femoral heads into the pelvic cavity.

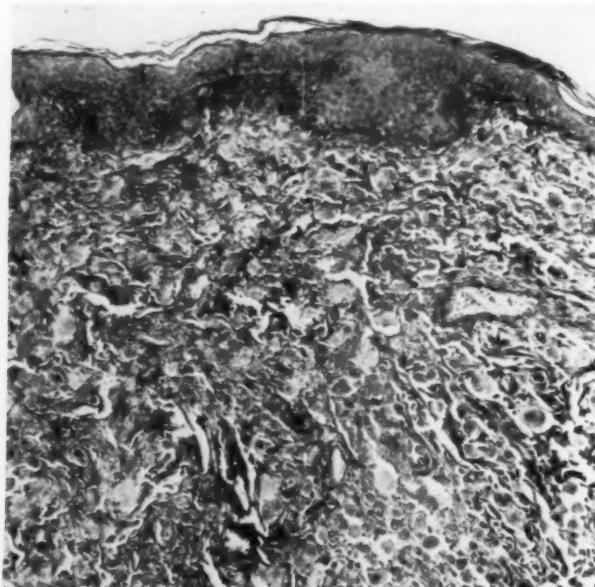


FIG. 7. Low power view of cutaneous lesion showing numerous lipoid-laden giant cells infiltrating the dermis.

The following studies were negative or normal: serologic test for syphilis; blood uric acid; slide and serum latex tests for rheumatoid arthritis; L.E. preparation; white blood cell and differential count; protein-bound iodine; calcium, phosphorus and alkaline phosphatase; fasting blood sugar; bromsulfalein dye excretion; routine urinalysis; twenty-four-hour urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids.

Roentgenograms demonstrated severe deformity of the hands and wrists. (Fig. 5.) There was widening of the interphalangeal joints due to destruction of the joint cartilage and subarticular bone. The joint spaces between the carpal bones were lost and some of the carpal bones were fused. Roentgenograms of the

hips revealed narrowing of the femoral heads and protrusion of the femurs into the pelvic cavity. The hip joints were ankylosed and destroyed. (Fig. 6.) Similar destructive changes were present in the knees, elbows and ankles. The skull and chest films were within normal limits. Diffuse osteoporosis was present in all the bones. A fracture was present in the distal third of the right tibia.

Histological and histochemical studies were performed on twenty cutaneous nodules and on a biopsy specimen of synovial tissue from the joint of the left wrist. Well developed nodules were composed of a moderately circumscribed dermal infiltrate of histiocytes, multinucleated giant cells and numerous blood vessels. (Fig. 7.) Occasionally, patchy mid-dermal infiltrates of lymphocytes were also present. The giant cells (up to 50 microns in diameter) possessed abundant, non-foamy, eosinophilic cytoplasm with a homogeneous or finely granular appearance. They contained up to 15 vesicular nuclei with prominent nucleoli. The dermal infiltrate was sharply demarcated from the intact epidermis by a narrow zone of normal collagen. The subcutaneous fat was not involved.

An early lesion contained few or no giant cells but was composed of a dense dermal infiltrate of numerous histiocytes, eosinophils, lymphocytes, blood vessels and extravasated red blood cells.

The synovial tissues contained numerous histiocytes, giant cells and blood vessels. (Figs. 8 and 9.) The giant cells were similar to those seen in the cutaneous nodules.

Biopsy of the liver and bone marrow revealed no abnormalities.

Histochemical staining of formalin-fixed cutaneous nodules revealed the following findings: frozen sec-

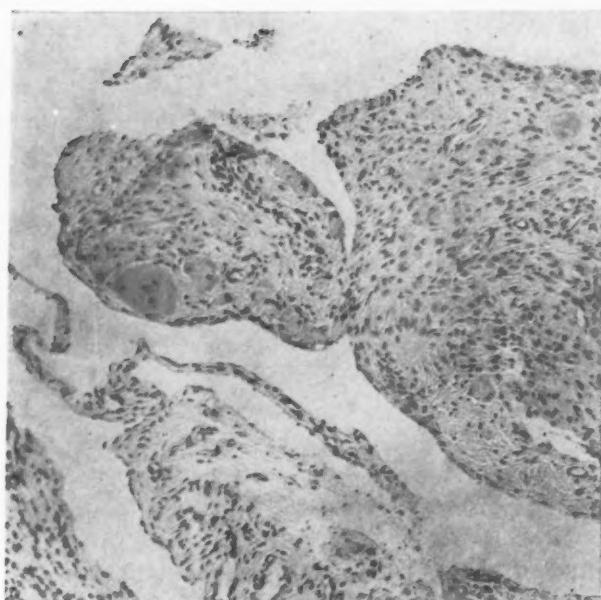


FIG. 8. Low power view of synovial tissue from left wrist. Numerous histiocytes, giant cells and blood vessels are present in the infiltrate.

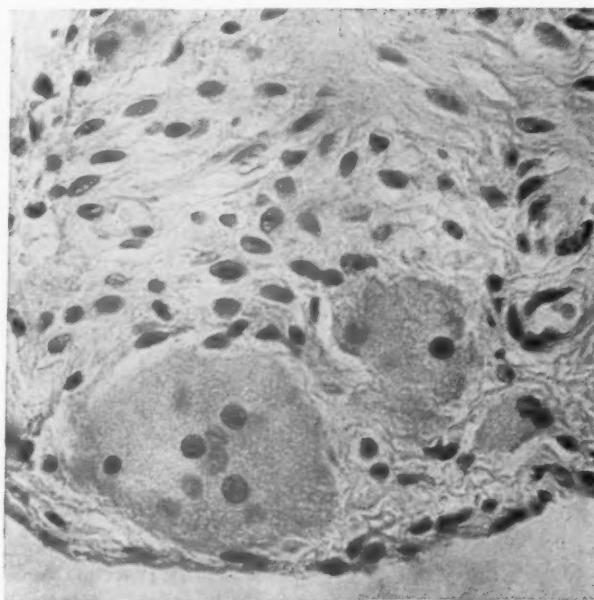


FIG. 9. High power view of giant cells lining the synovial space. The giant cells possess abundant, eosinophilic, finely granular cytoplasm and may have 1 to 15 nuclei.

tions stained with Sudan IV and oil red O showed only faint diffuse staining of the giant cell cytoplasm in most nodules but a few exhibited more intense staining. There was no increase in Sudan IV staining after 0.1N HCl hydrolysis. Frozen sections and post-chromed paraffin sections stained with Sudan black B showed moderate to intense staining. Periodic acid-Schiff (PAS) with or without diastase showed moderately intense staining of the giant cell cytoplasm and surrounding connective tissue which was abolished after extraction of the tissue with hot acetone. Prussian blue iron stain twenty-four hours after injection of 0.14 cc. colloidal iron revealed a small quantity of iron in giant cells, a large quantity in histiocytes. The following reactions were negative: Baker's acid hematin test; alcian blue; Millon's stain; thionine stain; Prussian blue for iron; Giemsa stain; Ziehl-Neelsen acid-fast stain.

The patient's fracture healed after three months in a plaster cast. Forty milligrams of triamcinolone was given for six weeks. There was temporary disappearance of some cutaneous nodules but they recurred when the administration of triamcinolone was stopped. There was only partial relief of arthritic pain and a slight increase in joint mobility.

COMMENTS

We have observed that early lesions may contain few or no giant cells and are composed of a dense dermal infiltrate of numerous histiocytes, lymphocytes and eosinophils. There are an increased number of blood vessels, and extravasated red blood cells may be observed lying

free in the tissues. Walther [6] recently has also observed a polymorphous infiltrate in some nodules. In addition to our findings of histiocytes, lymphocytes and eosinophils, he also noted the presence of plasma cells.

It is the opinion of one of us (A. C. A.) that this disorder has been called "ganglioneuroma" on one occasion because of the resemblance of the giant cells to ganglion cells [7].

We have concluded from our histochemical studies that the lipid substance present in the cytoplasm of the giant cells is probably a glycolipid; in this we concur with the findings of Lyell and Carr [7]. We came to our conclusion in the following manner: In most nodules the giant cell cytoplasm was only slightly stained with Sudan IV and other neutral fat stains, although some nodules showed stronger sudanophilia. The giant cell cytoplasm was more intensely stained with Sudan black B. This led to the conclusion that a bound or combined lipid was present in the giant cells. Unlike the red Sudan dyes which stain mainly neutral fat, Sudan black B also stains phospholipids, glycolipids, lipoproteins and lipofuscins [8].

There was also moderate staining of the giant cell cytoplasm and surrounding tissues by the periodic acid-Schiff (PAS) reaction which demonstrates the presence of 1,2 glycol groups. After extracting the tissue with hot acetone, a lipid solvent, the giant cells were no longer PAS-

positive. This indicated that the positive PAS reaction was due to a lipid substance. The only substances known to be stained by both the PAS reaction and Sudan black B are the glycolipids, phospholipids, lipoproteins and lipofuscins [8]. It remained to determine which of these substances was present in the cytoplasm of the giant cells.

The presence of lipofuscin, a pigment derived from the breakdown of lipoproteins, was ruled out because the giant cells lacked pigment, were eosinophilic and were not acid-fast. The presence of lipoprotein or a lipid-polypeptide complex was eliminated because there was no increase in Sudan IV staining following acid hydrolysis. In addition, the Millon reaction for proteins containing tyrosine was negative.

We then had to determine whether the positive PAS and Sudan black B reactions were due to phospholipids or glycolipids. There is no specific method for glycolipids and so several nodules were subjected to Baker's acid hematin method for phospholipids. Since phospholipids were not demonstrated we must conclude that the positive PAS and Sudan black B staining was probably due to the presence of a glycolipid in the giant cells and surrounding tissues.

The PAS-positive material was still positive after treatment with diastase, excluding the presence of glycogen. Acid mucopolysaccharides and mucoproteins were excluded by negative alcian blue and Millon stains and by a positive Sudan black B stain.

Caro and Senear [9] demonstrated phagocytosis of intravittally injected colloidal iron by the giant cells and considered this to be proof of the reticuloendothelial nature of these cells. Only small amounts of injected colloidal iron were ingested by the multinucleated giant cells in our studies. Larger amounts of iron, however, were ingested by small and large transitional histiocytes present in the same lesions. Staining with Prussian blue prior to iron injection revealed no normally occurring iron in the giant cells or surrounding tissues.

The serum cholesterol has been slightly or moderately elevated in one-third of the recorded cases, including our own. In other patients the serum cholesterol values were normal. Little attention has been paid to the total blood lipids or serum lipoproteins in this disease. Montgomery et al. [10] reported a normal total blood lipid value of 458 mg. per cent in one patient and values of 507, 616 and 756 mg. per cent in an-

other, who also had myxedema. Lyell and Carr [7] noted a slightly increased amount of alpha lipoprotein and a greatly increased amount of beta lipoprotein in a morning specimen of serum. An afternoon serum specimen, however, showed a normal amount of alpha and beta lipoprotein in their patient. Our patient's serum was not turbid. Analyses of her blood lipids, however, showed slight but distinct abnormalities. These included moderate elevation of the total blood lipids and cholesterol, transient elevation of the phospholipids and fatty acids, and an abnormal electrophoretic lipoprotein pattern. The latter finding was of especial interest, and increases the evidence in favor of a generalized disturbance of lipid metabolism in this disease. The plasma lipids are transported in combination with protein as lipoprotein [11] and a general disturbance in lipid metabolism may be reflected in an abnormal serum lipoprotein pattern. By paper electrophoresis two main lipoprotein bands normally appear, beta lipoprotein migrating with the beta globulin, and alpha lipoprotein migrating with the alpha-1 globulin of the protein pattern. At the origin the neutral fats are stained. The beta lipoproteins contain most of the cholesterol and are also rich in phospholipid. Our patient's pattern showed an increased quantity of beta lipoprotein. In addition, an abnormal band appeared, migrating ahead of the beta lipoprotein, toward the alpha-2 globulin level of the protein pattern. This abnormal band does not occur in hypercholesterolemic xanthomatosis [12]. The lipoprotein pattern of idiopathic hyperlipemia shows diffuse intense staining of neutral fat at the origin of the paper and the intense staining may extend to the alpha-2 globulin level of the protein pattern [12]. An increased quantity of beta lipoprotein is a feature of essential hyperlipemia [13]. A pattern similar to that seen in our patient occurs in other disturbances in lipid metabolism, such as the nephrotic syndrome, and may appear in coronary thrombosis [13]. Our patient had none of these diseases, however.

Further analyses of blood lipids and lipoprotein patterns in lipoid dermatitis may help elucidate the nature of the general lipid disturbance that we believe is present in this condition.

SUMMARY

1. Lipoid dermatitis is a recently recognized disease of lipid metabolism char-

acterized by a destructive polyarthritis resembling rheumatoid arthritis and by cutaneous papules and nodules.

2. Characteristic multinucleated giant cells are found in both the affected skin and synovial tissues.

3. The giant cells contain a lipid substance which is probably a glycolipid.

4. Early lesions may contain no giant cells but a polymorphous dermal infiltrate of histiocytes, eosinophils, lymphocytes and extravasated red blood cells.

5. The blood lipids may be normal or slightly elevated.

6. An abnormal electrophoretic lipoprotein pattern is demonstrated.

7. Treatment is unsatisfactory. Administration of corticosteroid hormones may cause temporary regression of the skin nodules but have little effect on the arthritis.

Acknowledgment: We wish to thank Mr. David Taplin for performing the histochemical staining, and Mr. William Atkinson and his staff for the photography.

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Chronic Relapsing Pancreatitis with Extensive Subacute Peritonitis and Chronic, Recurrent Massive "Chylous" Ascites*

EARL E. GAMBILL, M.D., WALTMAN WALTERS, M.D. and PAUL W. SCANLON, M.D.

Rochester, Minnesota

TRANSIENT, low grade ascites may occasionally develop during an episode of acute pancreatitis. Chylous-appearing ascites in this disease is rare. We have not seen any cases other than the one we are reporting herein, nor have we seen reports of ascites recurring over a six-month period following an attack of acute pancreatitis. Actually, exploration in our patient disclosed chronic pancreatitis with extensive diffuse peritonitis apparently due to pancreatitis. That such ascites, recurring during a six-month period, should cease after abdominal exploration without definitive surgical treatment but with x-ray therapy seemed unusual. Because of these unusual features we are reporting this case.

REPORT OF CASE

A fifty-four year old married insurance clerk came to the Mayo Clinic on September 4, 1954, because of ascites and edema of his legs of six months' duration. He had been drinking 4 to 6 ounces of whiskey daily for many years prior to December 1953 when he discontinued the consumption of alcohol. Since 1944 his weight had decreased gradually from 160 to 135 pounds. During 1953 he had had several episodes of abdominal bloating with pain, each lasting several days. Then on December 29, 1953, he had an acute, more severe episode of pain in the epigastrium and right upper quadrant that extended to the right lumbar region and was associated with a temperature of 101°F., nausea and vomiting (coffee-colored vomitus on one occasion), increased sedimentation rate, gastrointestinal ileus with distention, and serum amylase values of 256, 284 and 230 units. After two weeks of these symptoms the patient was hospitalized for three weeks and treated with gastric suction and intravenously administered fluids, electrolytes, glucose and vitamins. Gradual improvement followed his dismissal from the hospital until late February 1954 when ascites and edema of the legs developed.

Six thousand cubic centimeters of "chylous" fluid was removed by abdominal paracentesis. Since then paracentesis at four week intervals had been necessary, each time with removal of 8,000 to 10,000 cc. of the same chylous type of fluid, which did not contain malignant cells. The last paracentesis was performed two weeks prior to this admission. His physician had suspected abdominal malignancy with obstruction of the thoracic duct.

Physical examination disclosed a severely emaciated man with ascites, grade 2, and pitting edema of the legs, grade 2 to 3. The blood pressure was 96 mm. Hg systolic and 70 mm. Hg diastolic; the pulse rate was 100 beats per minute and the temperature 98.6°F. One spider angioma was seen over the left arm. There were prominent veins over the abdomen and flanks, and palmar erythema, grade 2, was present. It was thought that the liver was not enlarged, but ascites did not permit a good examination. The spleen was not palpable. A small hernial sac was felt in the left inguinal canal.

The patient had grade 1 albuminuria. The concentration of hemoglobin, erythrocyte and leukocyte counts, concentration of blood urea, concentration of blood sugar after fasting, results of the sulfobromophthalein test of liver function, concentration of serum bilirubin fractions, cephalin-cholesterol flocculation reaction and the Quick prothrombin time were all within normal limits. The concentration of serum protein was 4.9 gm. per 100 ml. (albumin 3.2 gm. and globulin 1.7 gm.). The sedimentation rate (Westergren method) was 49 mm. Electrocardiographic examination did not reveal any diagnostic defects. Results of the roentgenographic examination of the thorax were negative. A plain roentgenogram of the abdomen disclosed no calcific shadows. A few gas-containing loops of jejunum were seen in the left side of the abdomen. Studies of the esophagus and stomach with the aid of barium did not show varices. A tiny diverticulum was seen in the first part of the duodenum.

The patient was given a salt-poor, liver disease type

* From the Sections of Medicine, Surgery and Therapeutic Radiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is part of the Graduate School of the University of Minnesota.

of diet plus vitamin supplements. The caloric intake varied from 1,600 to 2,200 calories. Diuresis did not follow administration of 2 cc. of mercaptomerin (Thiomerin®) given on two different days.

At abdominal exploration on September 15, 1954, 3,000 cc. of "chylous ascitic fluid" was removed. The fluid appeared milky and contained flakes of calcium a few millimeters in diameter; some of the flakes were adherent to the visceral peritoneum. The visceral and parietal peritoneum throughout the abdomen presented a diffuse inflammatory reaction characterized by redness, edema and petechial hemorrhage on manipulation of the visceral structures. The pancreas was foreshortened, hard and reddened, having the typical gross size and feel of chronic pancreatitis. It was thought that a small tumor might be present in the head of the pancreas and obstructing the superior mesenteric vessels. Multiple specimens removed from this part of the pancreas all showed chronic pancreatitis. Specimens removed from the gastrocolic omentum and parietal peritoneum revealed subacute inflammation. The liver appeared normal. A biopsy specimen of the liver showed only organizing subacute exudate on the surface with mild pericholangitis. The ascitic fluid contained inflammatory elements with phagocytosed fat globules; culture was negative for brucella, fungi and tubercle bacilli, and guinea pig inoculation also was negative for tubercle bacilli.

Aside from considerable edema of the legs associated with low values for serum proteins, which seemed to be benefited by blood transfusions, the postoperative course was uneventful. More or less empirically, the patient was given roentgen therapy postoperatively; on each of four successive days, 160 r (air) was delivered to each of four anterior abdominal quadrants covering the entire peritoneal cavity. He was dismissed from the hospital on the twenty-fifth postoperative day. On October 14, 1955, a year after dismissal, he wrote that he felt more like his normal self again except for easy fatigability. He had been working every day since April 1955. Striking improvement in his appearance is shown in the photographs he sent us. (Fig. 1.)

The patient returned to the clinic on April 16, 1958, for a check-up. He had had no further attacks of abdominal pain or ascites since dismissal in October 1954. By April 1955, he had gained about 19 pounds and had returned to his usual work. He drank about two cans of beer daily. By mid-afternoon he would become fatigued. Although his appetite was good, food tasted flat. Since May 1957 he had felt full and gassy after eating small amounts and had noted persistent numbness of the tongue, upper and lower lips but no numbness of the extremities. Because of restricted intake of food he had lost about 8 pounds in a year. There was no history of steatorrhea and the bowel movements were regular.

On April 18, 1948, the patient weighed 116 pounds

APRIL, 1960



FIG. 1 Appearance of patient before (left) and one year after (right) exploratory laparotomy and roentgen therapy.

and was 72 inches tall. Blood pressure, temperature and pulse rate were normal. He was moderately emaciated and his face was florid. A firm nodule 2 cm. in diameter was present in the lower pole of the right lobe of the thyroid. He appeared euthyroid. The abdomen was flat; no masses were felt; the liver was not enlarged and there were no enlarged veins over the abdomen, thorax or legs. There was grade 2 pitting edema involving the lower half of the legs.

Results of the 1958 examination were as follows: Urinalysis disclosed an occasional hyaline cast. Roentgenographic study of the thorax, pancreatic region, gallbladder and stomach revealed no abnormalities. The values for hemoglobin, leukocyte count, sedimentation rate, Quick prothrombin time, concentration of blood urea, fasting blood sugar, and values for fatty acids and total lipids were within normal limits. The value for total proteins was 5.1 gm. per 100 ml. (albumin 3.7 gm., and globulin 1.4 gm.). The serum carotene level was 16 I. U. per 100 cc. The serum calcium measured 8.7 and 8.5 mg. per 100 ml. and the phosphate 2.9 and 2.4 mg. per 100 ml. on two different days. A twenty-four-hour collection of feces while the patient was receiving a general diet contained 21 per cent of fat; the total weight of the specimen was 364 gm., of which 27 gm. represented solids.

It was thought that the decreased concentration of serum proteins was possibly due to decreased intake of protein and that the decreased concentration of serum calcium might in turn be related to the low concentration of serum proteins. The patient was dismissed with instructions to follow a high caloric, high protein diet with vitamin supplements, and to refrain from the use of alcoholic beverages.

COMMENTS

Unusual in this case is the fact that abdominal paracentesis was required for recurring ascites for as long as eight months after the attack of acute pancreatitis. The white, milky appearance of the fluid suggested that it was of chylous

origin and resulted from obstruction to the lymphatic ducts. Could this appearance have been due to hyperlipemia secondary to or associated with the pancreatitis, or due to a high fat content from breakdown of tissue fat by pancreatic lipase liberated as a result of pancreatitis? Unfortunately, we did not determine the blood fats or the fat content of the ascitic fluid during the patient's illness. The presence of phagocytosed fat globules in the fluid might favor a high fat content in the fluid. The values for blood fat were within normal limits approximately three and a half years after exploration.

The extensive diffuse subacute peritonitis in the absence of demonstrable infection is unusual. The appearance and diffuseness of the process are consistent with a chemical peritonitis such as might be produced by the prolonged presence of pancreatic enzymes in the peritoneal cavity. While the peritoneal process was subacute, the pancreatic process was chronic.

We believe that these striking features of chronic recurring chylous ascites over a six-month period, with diffuse subacute peritonitis and the gross and microscopic picture of chronic pancreatitis, represent unusual sequelae of chronic relapsing pancreatitis. Why ascites should first be observed about eight weeks after an acute episode of pancreatitis and then recur several times over a six-month period in the absence of further episodes of pain is obscure, although possibly the patient may have had subsequent recurrent episodes of so-called painless pancreatitis. Equally obscure is why such a chronic process, continuing for eight months, should clear up after exploratory laparotomy and roentgen therapy, since no specific therapeutic measures were carried out at surgical exploration by which such relief might be explained. Whether roentgen therapy had

anything to do with the favorable course remains speculative. Our records indicate that eight patients with chronic pancreatitis received roentgen therapy in the years 1936 to 1957, inclusive. The indication for treatment was pain, and none of them had ascites at the time. There was no clear-cut evidence that such therapy was definitely beneficial in relieving the pain of pancreatitis.

Morton and Widger [1] reported that roentgen therapy possibly may shorten attacks of acute pancreatitis. Streda [2] indicated that roentgen therapy was beneficial in chronic pancreatitis. Chisholm and Seibel [3] used roentgen therapy in dogs with experimentally produced acute pancreatitis and in normal dogs, and observed that a single exposure apparently inhibited production of amylase but that heavy or repeated doses may have had deleterious effects on the pancreas.

SUMMARY

A fifty-four year old man chronically addicted to the use of alcohol suffered from chronic relapsing pancreatitis. Peculiarly interesting is the appearance of chylous ascites eight weeks after a severe attack of pancreatitis which required repeated abdominal paracentesis for about six months. After exploration and roentgen therapy, ascites and pain had not recurred during the subsequent three years of observation.

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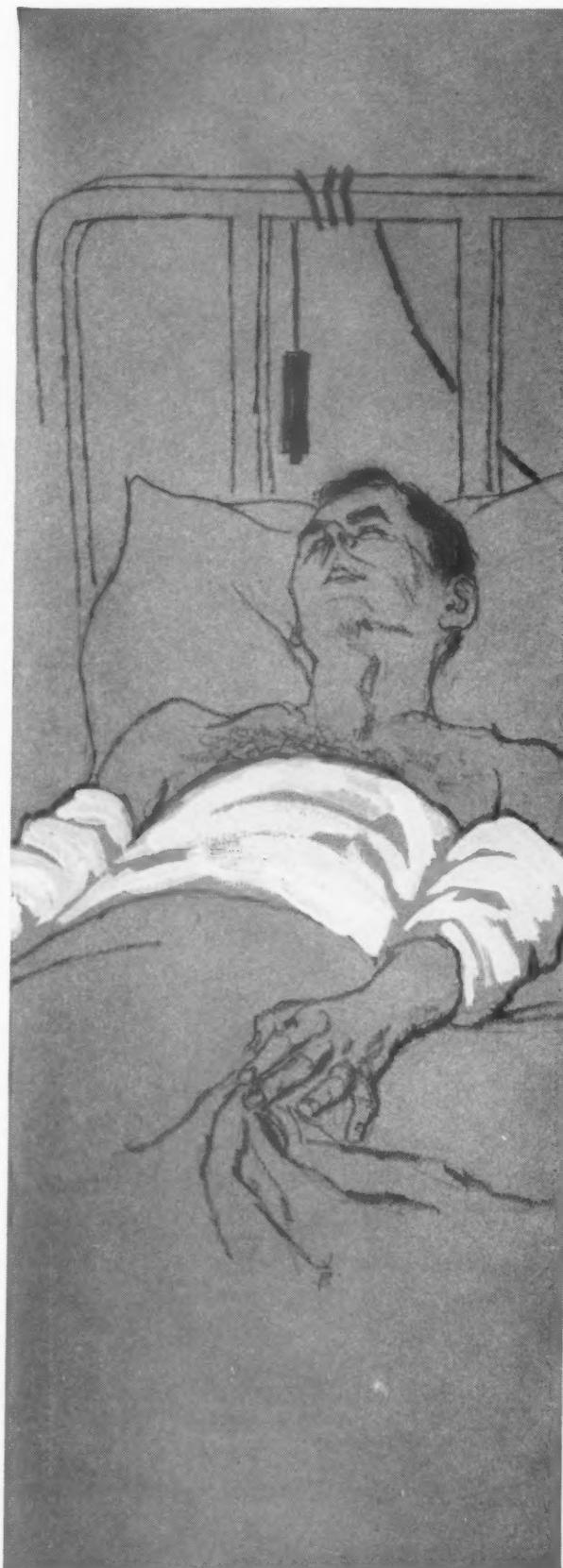
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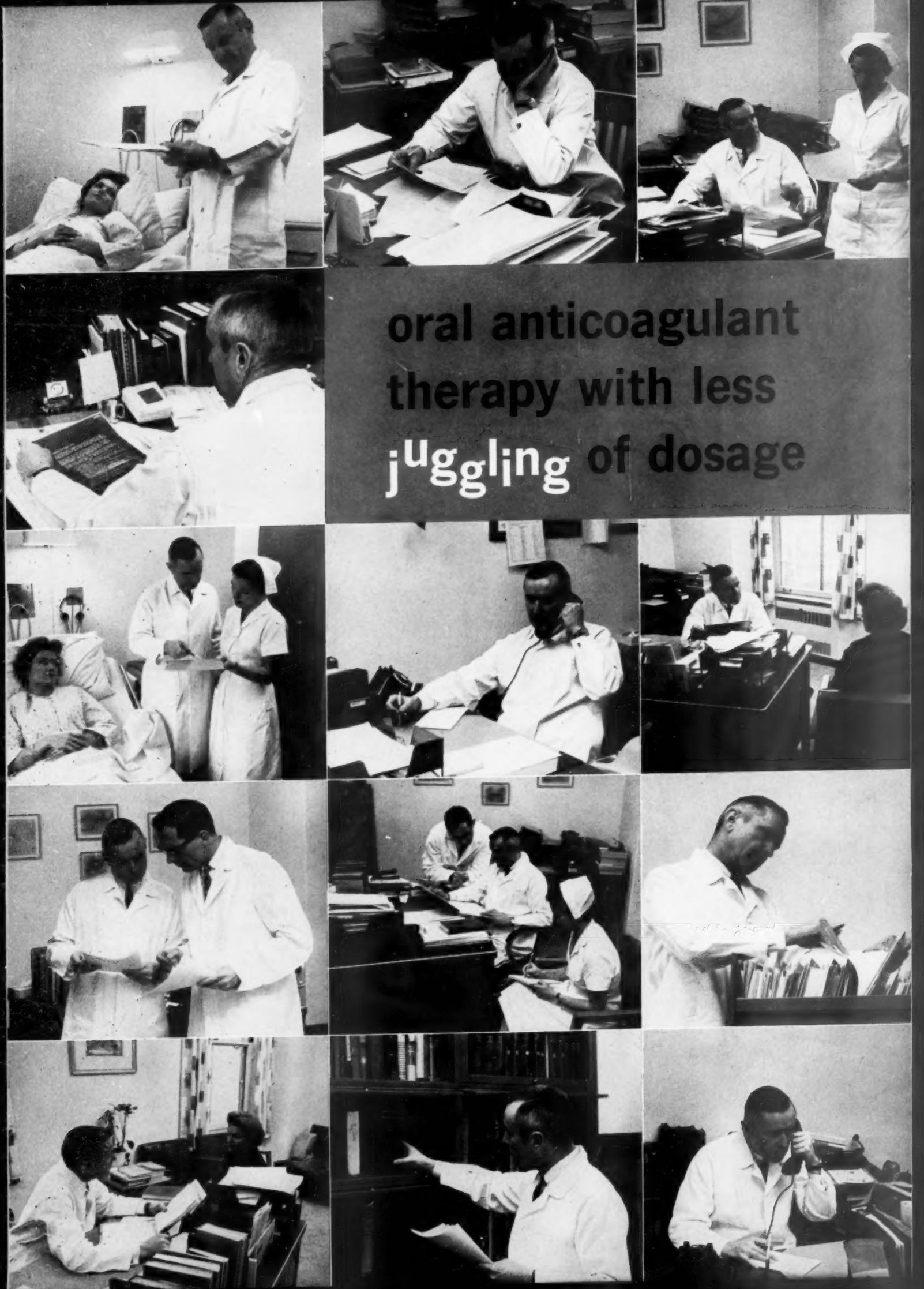
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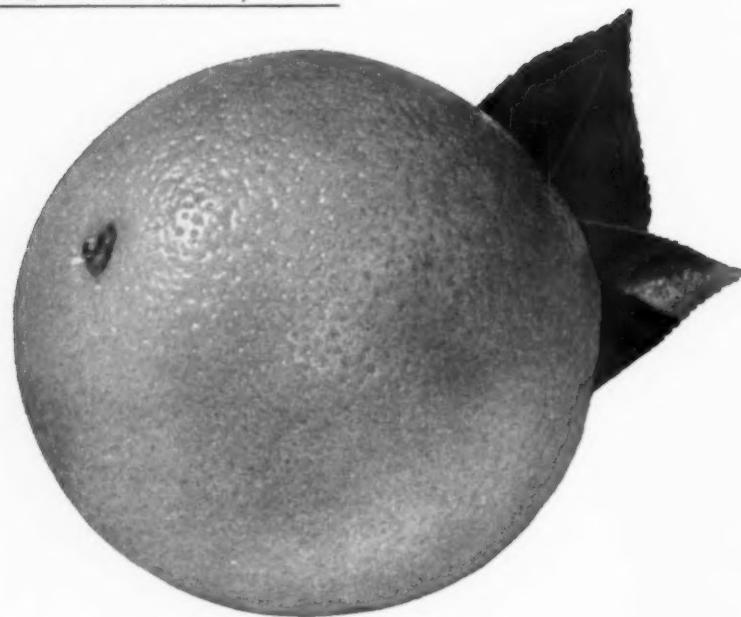
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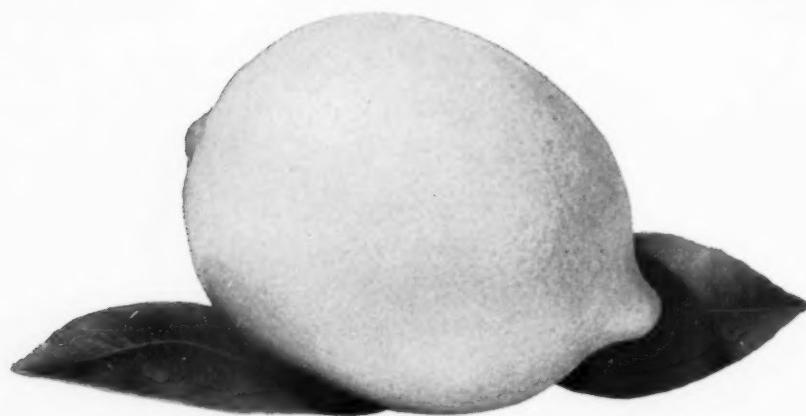
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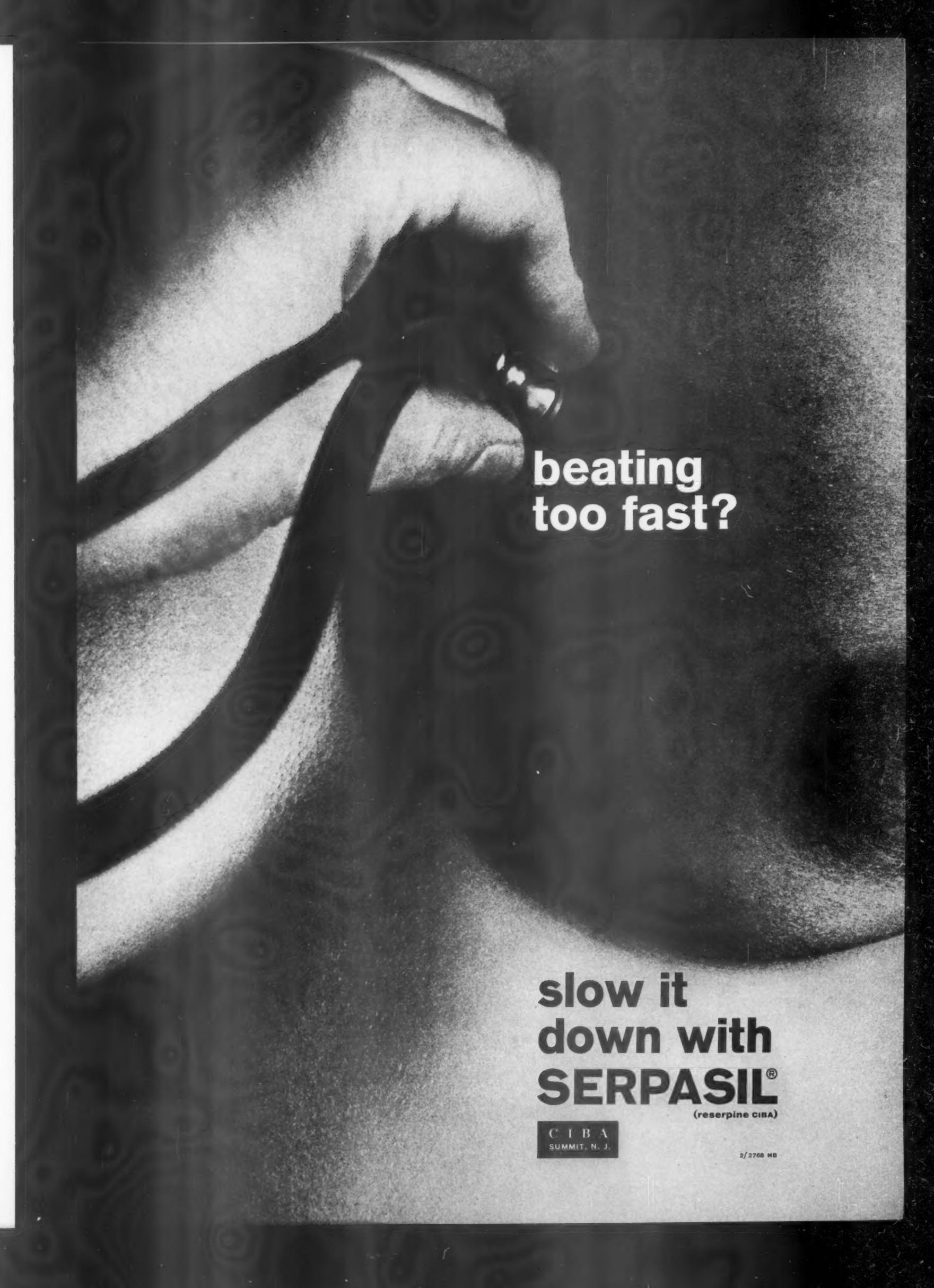
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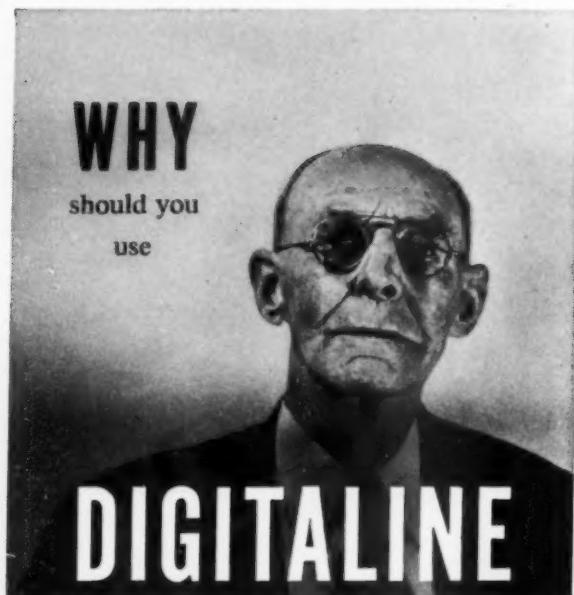
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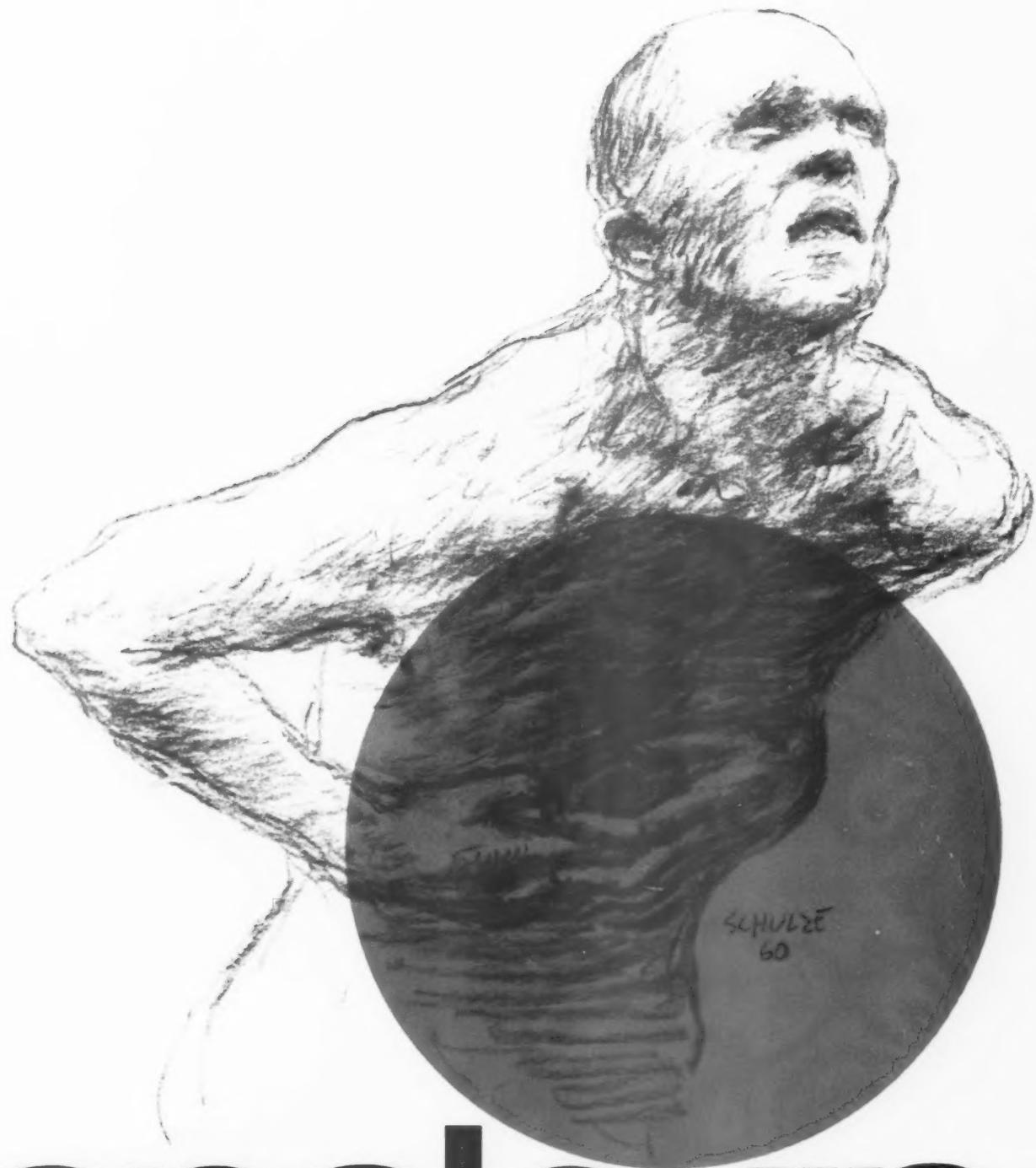
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hiatus hernia	1	1	
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dysmenorrhea	96	88	8
abdominal distress (flatulence, colic, constipation, etc.)	10	6	4
epigastric distress (pylorospasm, gastritis, etc.)	10	7	3
genitourinary pain	3	3	
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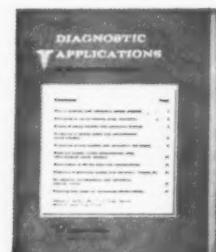
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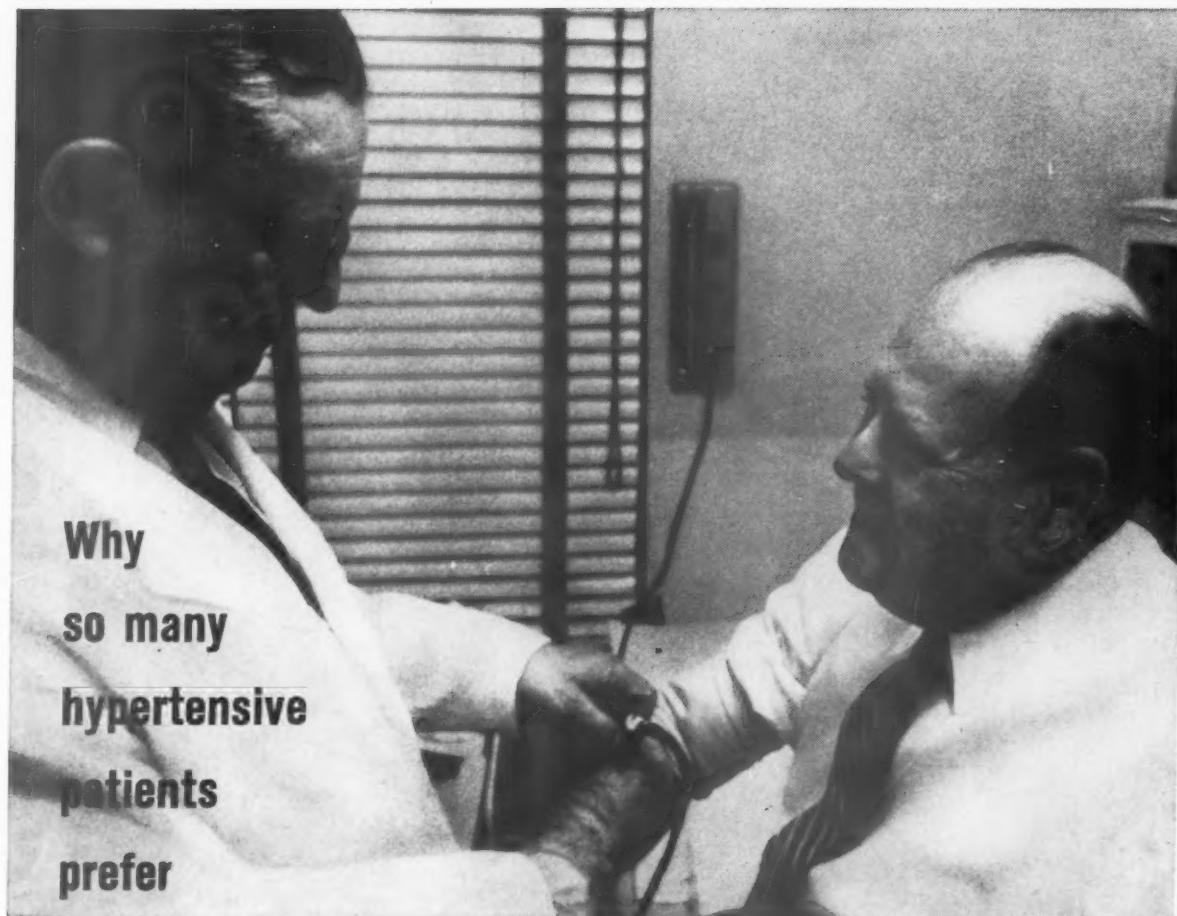
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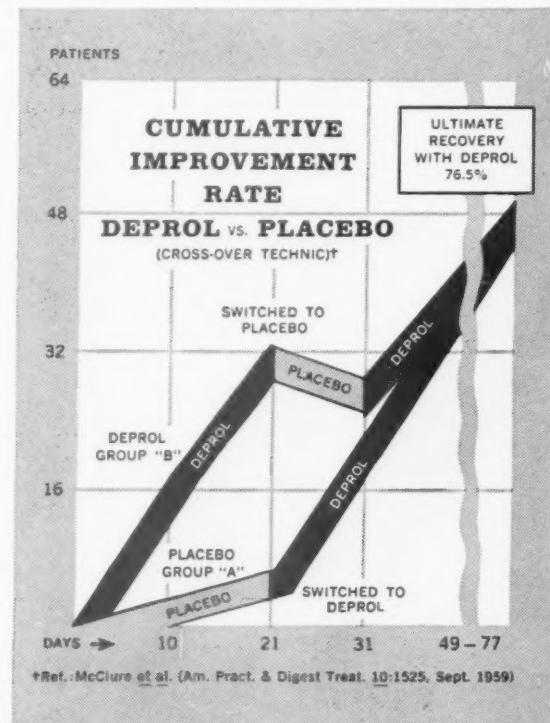
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1. Alexander, L. (35 patients): Chemotherapy of depression — Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958.
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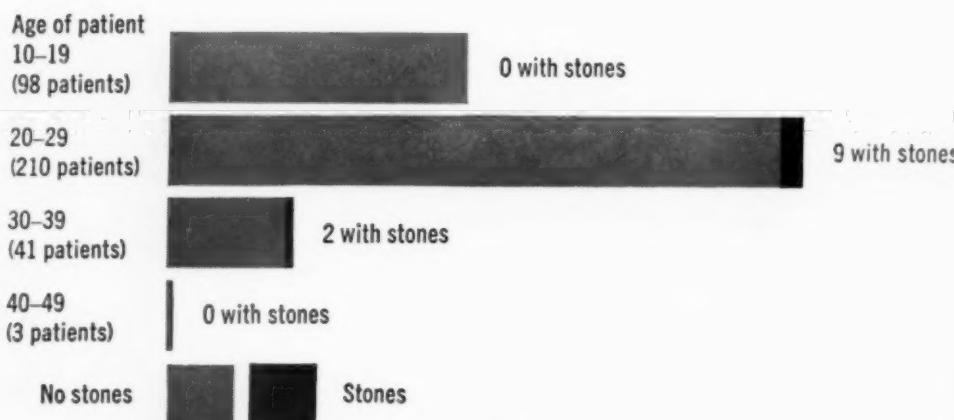


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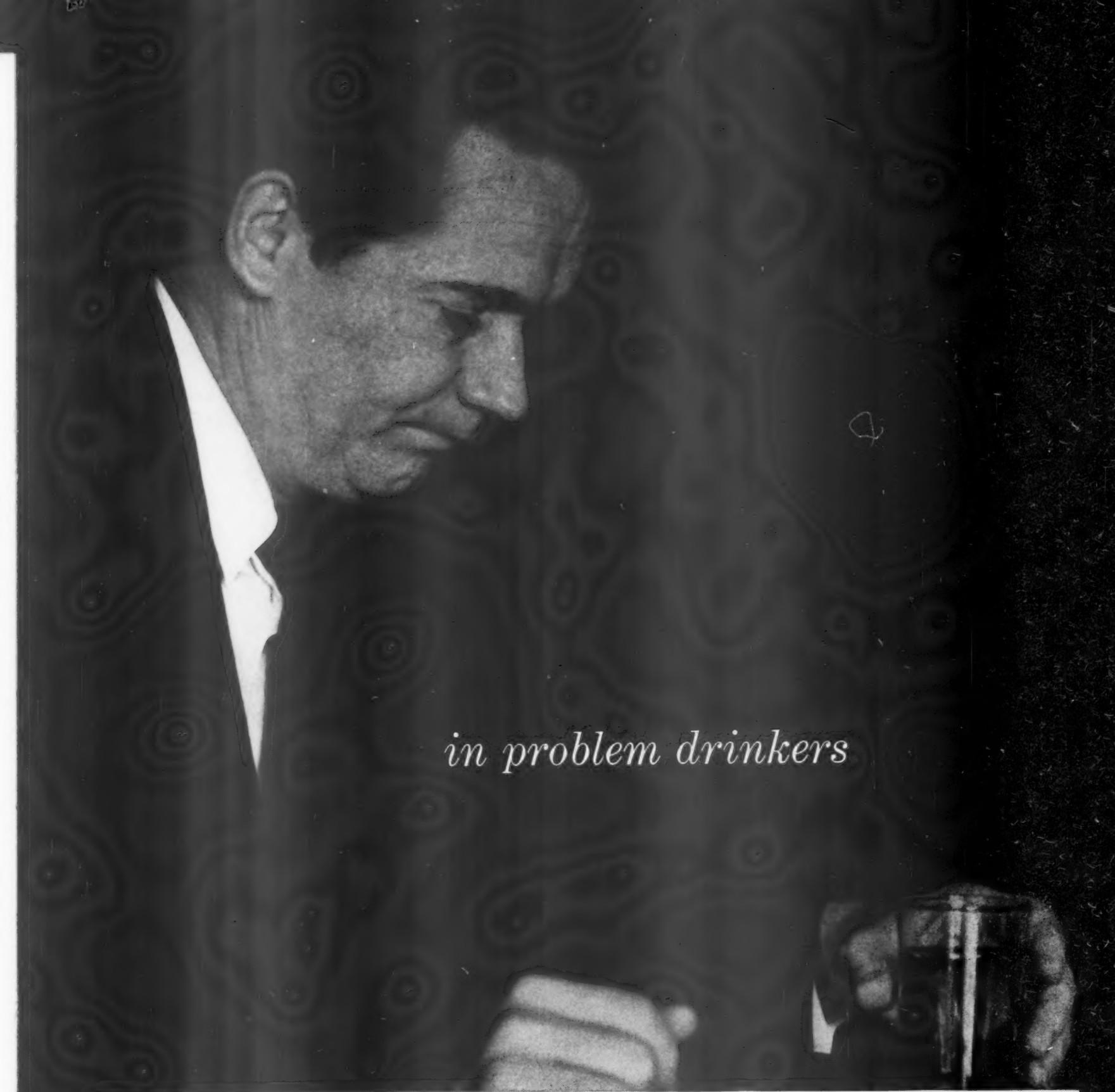
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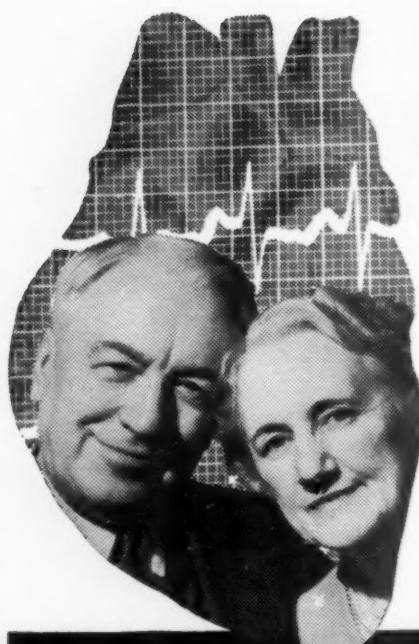
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1. Bellet, S.; Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med., 100:750, 1957.
2. Bellet, S.: Amer. Heart J., 56:479, 1958.

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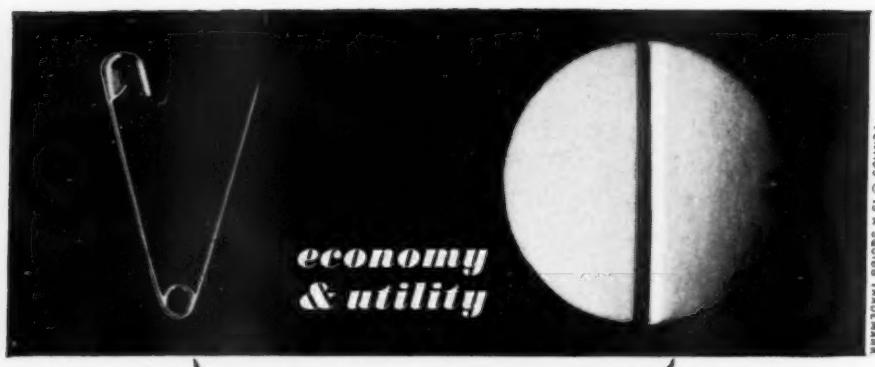
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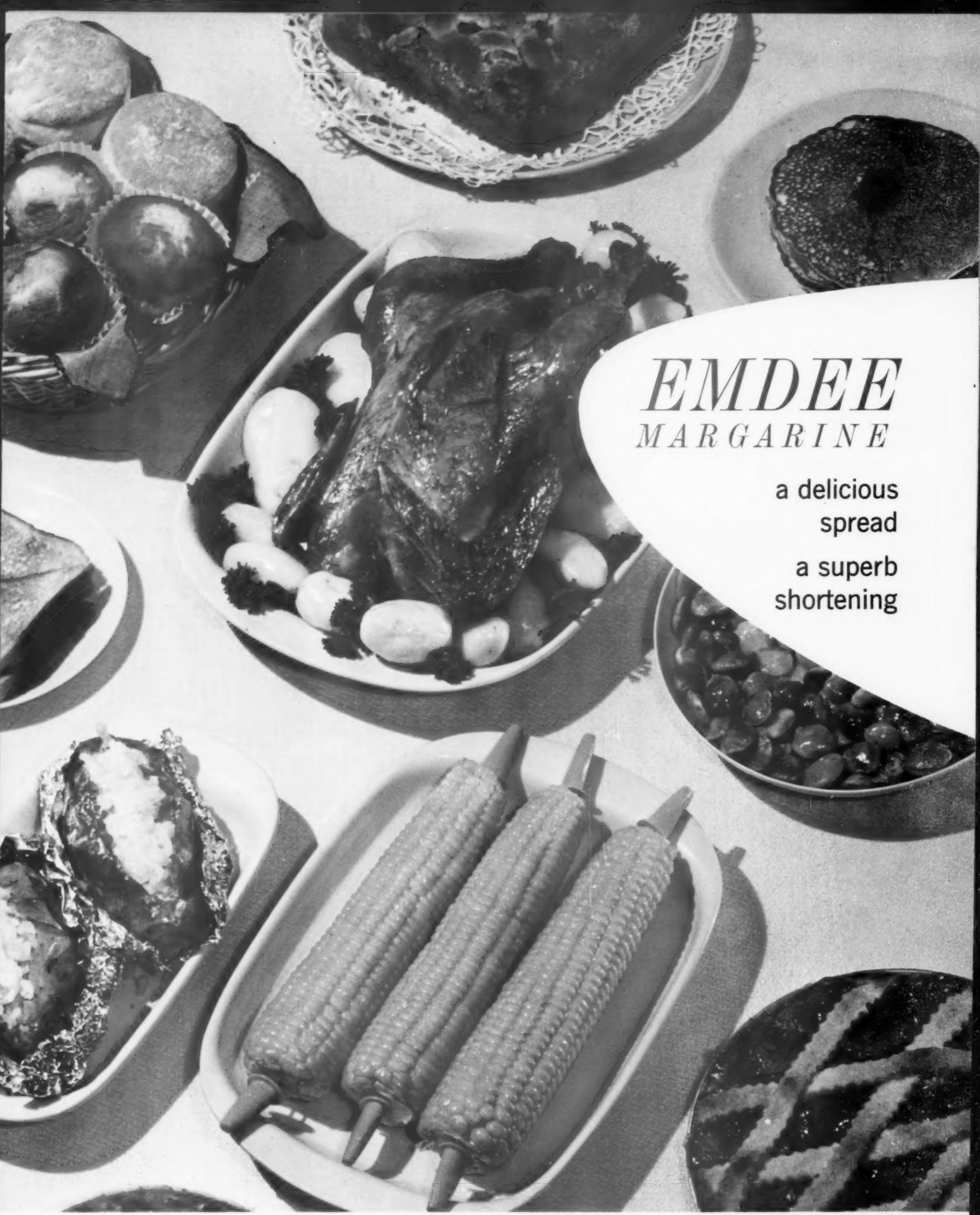
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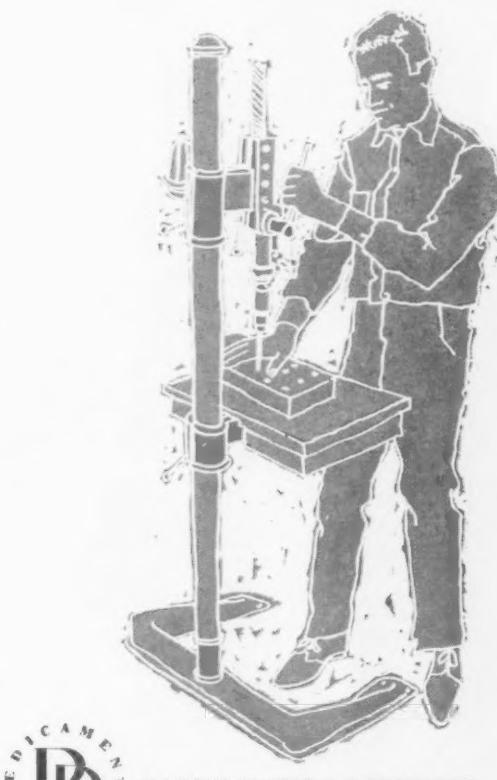
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WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of post-prandial lipemic serum."¹ Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.¹ It therefore provides important benefits for your postcoronary patients.

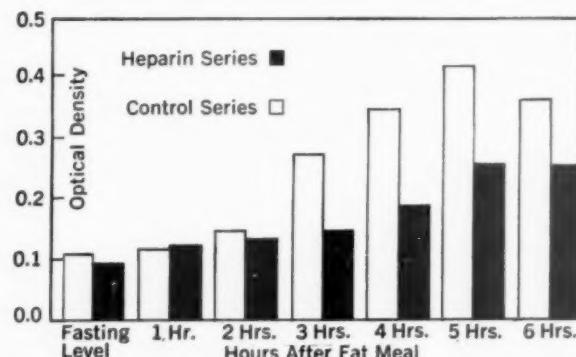
Indication: For the management of hypertension associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: *Angiology* 9:311 (Oct.) 1958.

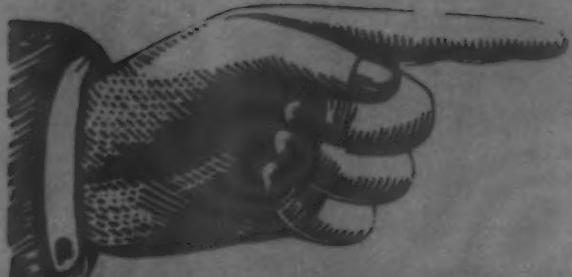
2. Shaftel, H. E., and Selman, D.: *Angiology* 10:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.²

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc. New York 17, N. Y.



Over 300,000,000 tablets of Obedrin have been administered since its introduction . . . enabling overweight patients to lose approximately 18,000,000 pounds of excess fat. (Studies show an average weight loss of 6 lbs. per 100 tablets. *)



Obedrin and the 60-10-70 Basic Plan provide the three essentials of weight reduction:

1

Supervision by A balanced
the physician eating plan

2

Supportive
medication

3

Obedrin curbs unhealthy food craving, enabling the patient to establish correct eating habits . . . first, to lose excess pounds and then, more important, to maintain optimum weight.

Each capsule or tablet provides:

	Semoxydrine® HCl (methamphetamine HCl), 5 mg., for its anorexigenic and mood-lifting effects
	Pentobarbital, 20 mg., to guard against excitation
	Thiamine Mononitrate, 0.5 mg., Riboflavin, 1 mg., and Nicotinic Acid (Niacin), 5 mg., to supplement the diet
	Ascorbic Acid, 100 mg., to help mobilize tissue fluids

* Eisfelder, Henry W.: Treatment of Obesity. The Role of the Doctor, Drug and Diet in Weight Loss, Am. Pract. and Dig. of Treat., 5:778 (Oct., 1954).
Sherman, Robert J.: Weight Reduction, Med. Times, 82:107 (Feb., 1954).

Obedrin



and the 60-10-70 Basic Plan
provide an effective weight-control regimen

Bristol, Tennessee • New York • Kansas City • San Francisco

THE S. E. MASSENGILL COMPANY

LOST & FOUND

OTHER LOST & FOUND—PAGE 1

LOST: lady's diamond engagement ring. Center diamond 90 points and 2 side diamonds. Initials "I.J.E." to J.I.A. D., 4/6/58." Vicinity 32d & Cincinatti sts., on Oct. 26. Liberal reward. V. E. Fisher & Sons, 1/11-5701.

LOST: Oct 30th. Vic Jefferson air hard Hotel & 30th Railroad Station. Gold clip-pin. Scroll design, rubies & diamonds. Liberal reward. Call collect Roanoke, Virginia. Dictions, 2-9323.

LOST: Men eve, U of P vic. Black male puppy, Kerry Blue Terrier. No collar. Left ear clued down. Lg rev. \$100 or \$100-5502.

LOST: 9,000 tons of human fat, by patients whose doctors prescribed Obedrin.

LOST: Penna Railroad Pass in wallet. Reward. Return to 1/11 Hill, 1d4 N 21st st or 2-2-1017.

LOST: Brown brief case cont Bibles, stop watch, etc, vic 15th & Girard. Reward. \$10. 11/10 12-2-7325.

LOST: Ladies' gold Omega watch, blue crystal, vic Veneracion's. Oct 31. Reward. 1/1/2-432E (N J).

LOST: Nov 3. Beaded black handbag. Gift of a co-worker sister. Rew. 1h 7-000. Vic Lester Jr High.

LOST: Star sapphire ring, 10/24, P.M., vic Ferrell doctor or center Hill, Roanoke, VA. 7-C71.

LOST: Black pocketbook, vic Irene's 3rd St. Reward. 1C E 575C, Ext 2.

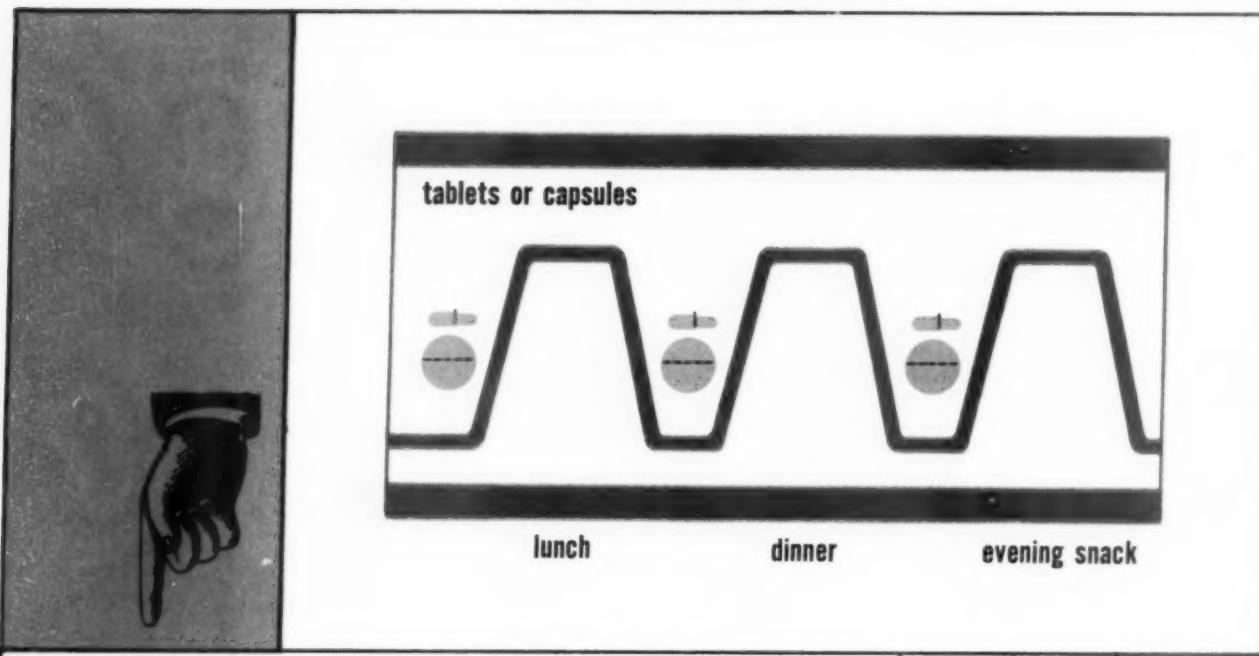
LOST: Green diamond watch on 14th st bet Sir John & Hill, Kew, G-274.

LOST: Bankbook #4-676. Joint M. Girard Corp Exchange, 2-4-952.

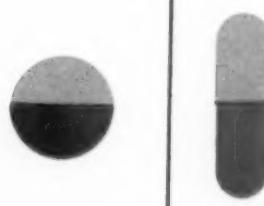
LOC:



A FLEXIBLE DOSAGE FORM PROVIDES DEPENDABLE CONTROL OF APPETITE

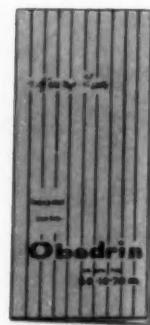


The Obedrin formula permits a flexible dosage schedule to depress the appetite at peak hunger periods. The physician can adjust dosage to fit each patient's need.



ADVANTAGES OF OBEDRIN—

- A dependable anorexigenic agent!
- A flexible dosage form!
- Minimal central nervous stimulation!
- Vitamins to supplement the diet!
- No hazards of impaction!!!



Write for 60-10-70 menus, weight charts, and Obedrin samples. Used with the 60-10-70 Basic Plan, Obedrin offers an ideal weight-control regimen for the overweight patient.



Obedrin®
and the 60-10-70 Basic Plan

Tofrānil®

brand of imipramine HCl

in depression

In the treatment of depression Tofrānil has established the remarkable record of producing remission or improvement in approximately 80 per cent of cases.¹⁻⁷

Tofrānil is well tolerated in usage—is adaptable to either office or hospital practice—is administrable by either oral or intramuscular routes.

**Tofrānil
a potent thymoleptic...
not a MAO inhibitor.**

Does act effectively in *all* types of depression regardless of severity or chronicity.

Does not inhibit monoamine oxidase in brain or liver; produce CNS stimulation; or potentiate other drugs such as barbiturates and alcohol.

Detailed Literature Available on Request.

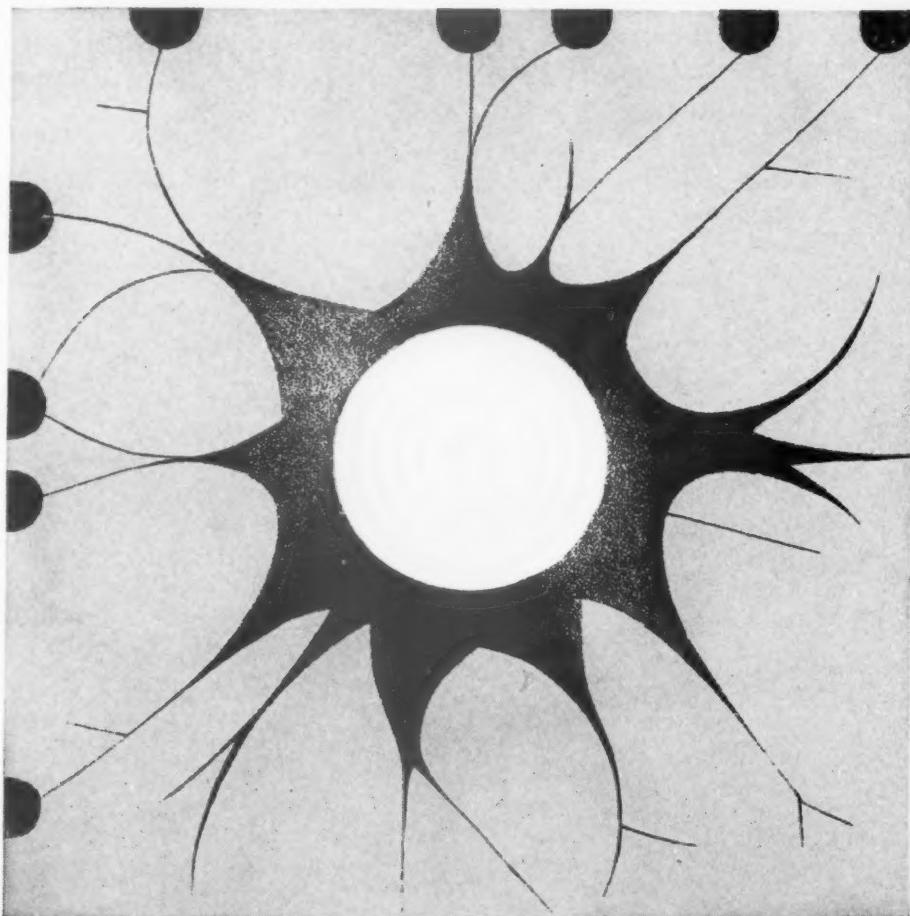
Tofrānil® (brand of imipramine HCl), tablets of 25 mg., bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution, cartons of 10 and 50.

References: 1. Ayd, F. J., Jr.: Bull. School Med. Univ. Maryland 44:29, 1959. 2. Azima, H., and Vispo, R. H.: A. M. A. Arch. Neurol. & Psychiat. 81:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M. A. J. 80:540, 1959. 6. Straker, M.: Canad. M. A. J. 80:546, 1959. 7. Strauss, H.: New York J. Med. 59:2906, 1959.

Geigy, Ardsley, New York



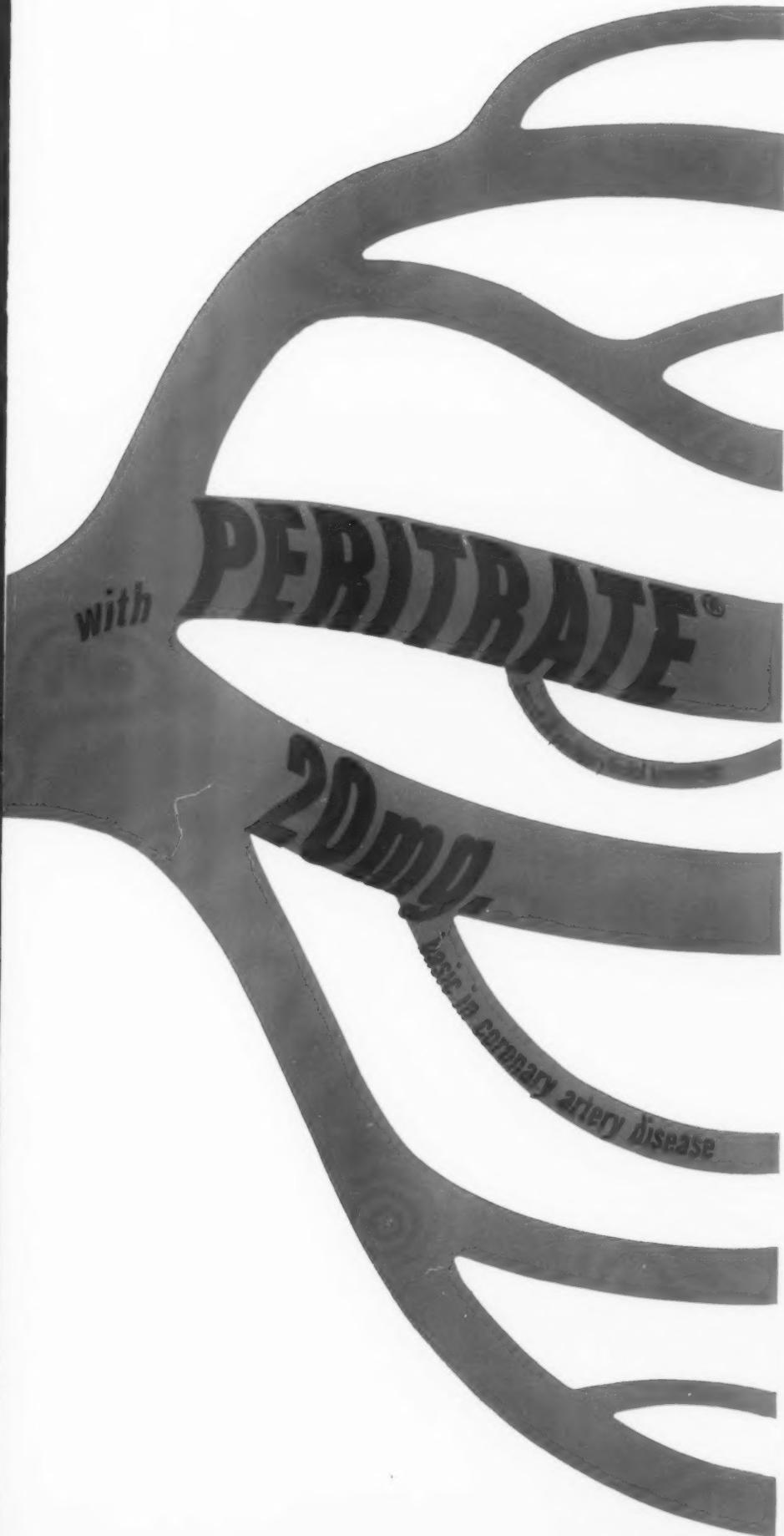
lights the road to recovery
in 80 per cent of cases



TO 4-60

Geigy

improve coronary blood flow in angina and postcoronary patients



■ a proven drug—

supported by extensive clinical experience during the last ten years

■ selective physiologic action—

unlike most nitrites, dilates coronary vessels principally, with minimal peripheral effects, so that coronary blood flow is increased with no significant change in blood pressure or pulse rate

■ exceptionally safe—

safe for prolonged use—essentially free from side effects—tolerance has not been reported—no hypotension, orthostatic or otherwise, has occurred—*so safe, it is used routinely even after a coronary*

■ effective in mildest to severest angina pectoris—

4 out of 5 patients experience reduced frequency and severity of anginal attacks, increased exercise tolerance, lowered nitroglycerin dependence, improved ECG findings

■ ideal in postcoronary convalescence—

helps establish and sustain collateral circulation to reduce the extent of myocardial damage, to encourage natural healing and repair, to minimize ensuing anginal attacks

■ adaptable prophylaxis—

available in several formulations to meet the individual requirements of patients with coronary artery disease: Peritrate 20 mg. for basic prophylaxis, Peritrate with Phenobarbital for the apprehensive patient, Peritrate Sustained Action for convenient 24-hour protection with just 2 tablets daily.



MORRIS PLAINS, N.J.

**first of a new class of therapeutic agents
for superior, safer, faster control
of common emotional disturbances**

in a class by itself—chemically

Not a manipulated molecule, the structure of this compound resembles that of no other drug. Librium is a product of truly original Roche research.

in a class by itself—pharmacologically

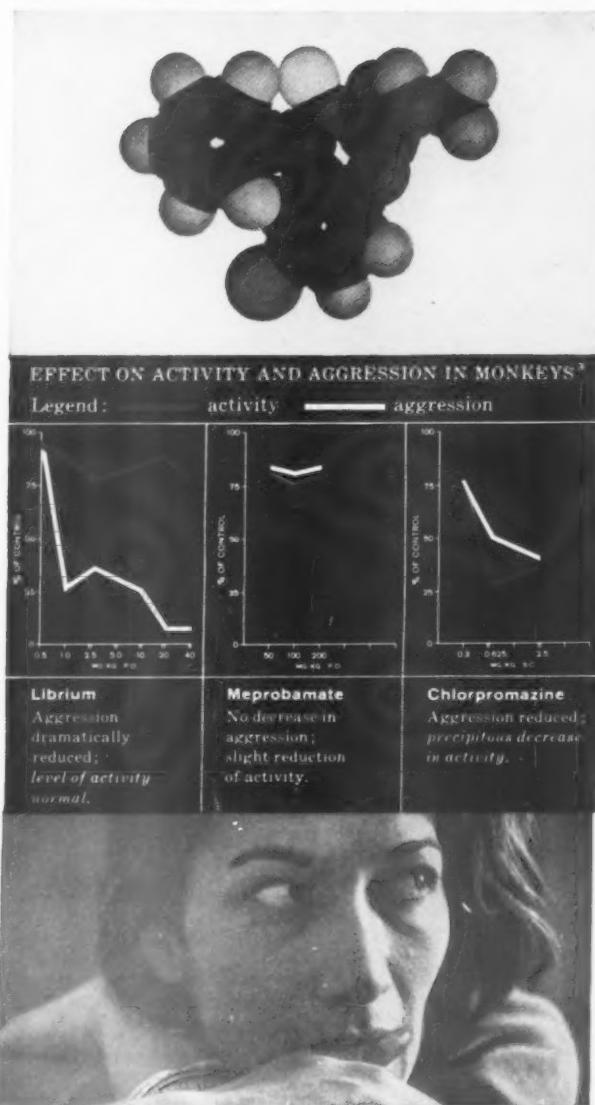
Librium exhibits an unprecedented "taming" action in animals. It is the first compound in which the specific antiaggressive component is separated from a generalized depressant effect on locomotor activity and reflex patterns. While Librium has tranquilizing properties comparable with those of chlorpromazine and reserpine, it lacks the autonomic blocking effects of these compounds and does not produce extrapyramidal side effects. Librium has none of the hypnotic effects of the barbiturates.

in a class by itself—clinically

The therapeutic range of Librium "envelops and extends well beyond that of meprobamate and into certain indications for which the phenothiazines are prescribed."¹ More than replacement therapy, Librium is quantitatively and qualitatively superior to "tranquilizers" and "equanimity-producing drugs." Librium is distinguished by an unusually rapid onset of action and a high degree of safety.

- Published reports on Librium:** 1. G. A. Constant, *Dis. Nerv. System*, 21:(Suppl.), 37, 1960. 2. T. H. Harris, *ibid.*, p. 3. 3. L. O. Randall, *ibid.*, p. 7. 4. H. A. Bowes, *ibid.*, p. 20. 5. J. M. Tobin, I. F. Bird and D. E. Boyle, *ibid.*, p. 11. 6. J. Kinross-Wright, I. M. Cohen and J. A. Knight, *ibid.*, p. 23. 7. H. H. Farb, *ibid.*, p. 27. 8. C. Breitner, *ibid.*, p. 31. 9. I. M. Cohen, *ibid.*, p. 35. 10. L. J. Thomas, *ibid.*, p. 40. 11. R. C. V. Robinson, *ibid.*, p. 43. 12. S. C. Kaim and I. N. Rosenstein, *ibid.*, p. 46. 13. H. E. Ticktin and J. D. Schultz, *ibid.*, p. 49. 14. J. N. Sussex, *ibid.*, p. 53. 15. I. N. Rosenstein, *ibid.*, p. 57. 16. I. N. Rosenstein and C. Silverblatt, to be published.

NEW LIBRIUM



LIBRIUM™ Hydrochloride —
7-chloro-2-methylamino-5-phenyl-1,4-
benzodiazepine 4-oxide hydrochloride
 **ROCHE**
LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N.J.

to free the patient

from anxiety and tension,
whether presenting symptomatology
or associated with
organic or functional disorders.

to free the therapy

from the drawbacks of
previous agents.

to free the physician

from the frustrations of prolonged,
inconclusive treatment and
to render the patient
more amenable to therapy.

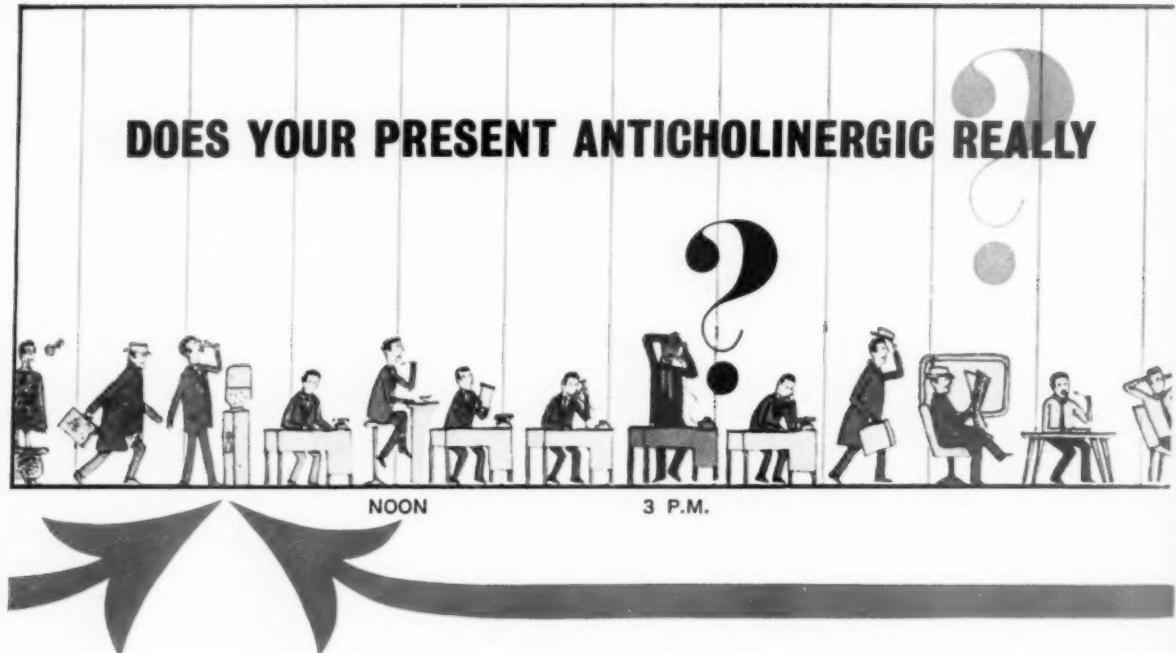
uses of Librium

in the office patient, troubled by
anxiety and tension, and
by the irritability, fatigue and
nervous insomnia associated
with tension states

in the office patient, where you
suspect anxiety and tension as
contributing or causative factors of
organic or functional disorders

in more severely disturbed patients,
including cases of agitated and
reactive depression, fears, phobias,
obsessions and compulsions

Supplied: 10-mg, green-and-black capsules.
Bottles of 50 and 500.
For complete information regarding
dosage and precautions, please
consult product literature.



The test—you might say the acid test—of an anticholinergic is simple: will it protect your patient from hyperacidity around the clock, even while he sleeps. The weakness of t.i.d. or q.i.d. preparations is well recognized; but even some "b.i.d." encapsulations may be unreliable. McHardy, for instance, found a "widely variable duration of action, definitely less than that anticipated" in the "sustained," "delayed," and "gradual release" anticholinergics he studied.¹

COMPARE THE DATA ON ENARAX... the new combination of an inherently long-acting anticholinergic (oxyphencyclimine) and Atarax, the non-secretory tranquilizer. Note the effectiveness of oxyphencyclimine:

OBSERVE THE OXYPHENCYCLIMINE REPORTS...

McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."¹

Kemp: "...for the majority of patients, one tablet every 12 hours provided adequate control. This characteristic long action...may constitute an advantage of this drug as compared to coated 'long-acting' preparations of other compounds."²

Add Atarax to this 12-hour anticholinergic. The resulting combination—ENARAX—now gives relief from emotional stress, in addition to a reduction of spasm and acid. Atarax does not stimulate gastric secretion. No serious adverse clinical reaction has ever been documented with Atarax.

LOOK AT THE RESULTS WITH ENARAX^{4,5}:

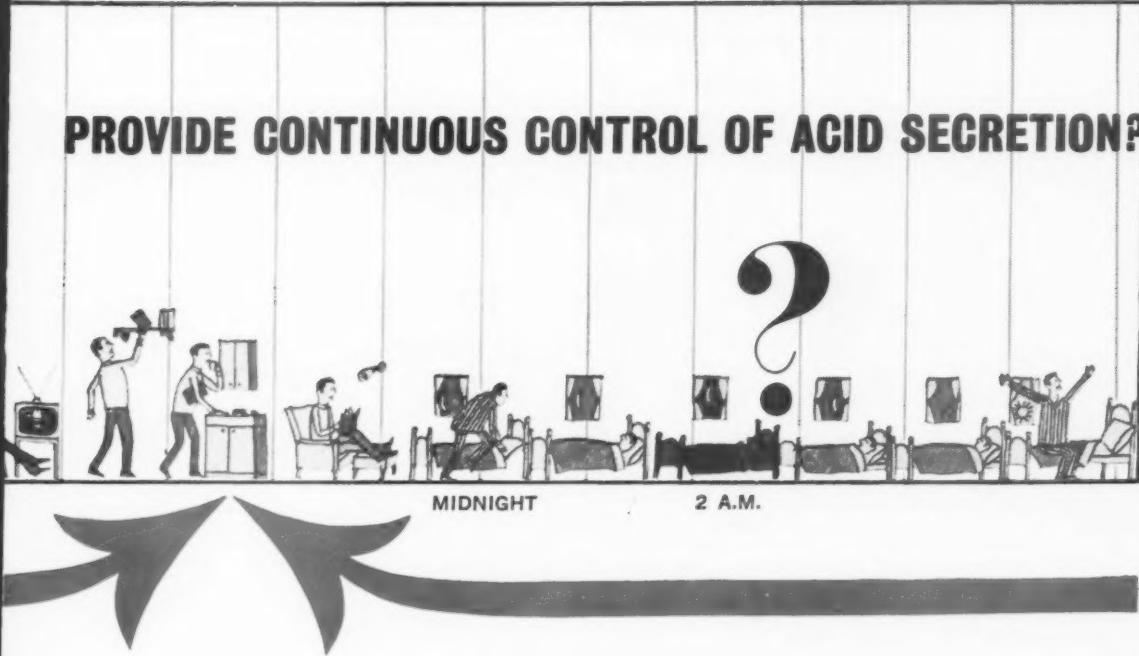
Does the medication you now prescribe assure you of all these benefits? If not, why not put your next patient with peptic ulcer or G.I. dysfunction on therapy that does.

ENARAX®

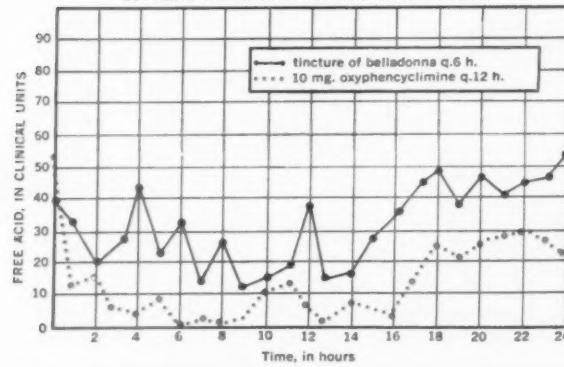
(oxyphencyclimine plus ATARAX®)

A SENTRY FOR THE G.I. TRACT

PROVIDE CONTINUOUS CONTROL OF ACID SECRETION?



"Prolonged periods of achlorhydria" after 10 mg. oxyphencyclimine q. 12 h.²
MEAN GRAPH OF GASTRIC ACIDITY IN 4 PATIENTS RECEIVING
COMPLETE THERAPEUTIC REGIMEN - 24-HOUR STUDY



Clinical Diagnosis: Peptic Ulcer — Gastritis — Gastroenteritis — Colitis — Functional Bowel Syndrome — Duodenitis — Hiatus Hernia (symptomatic) — Irritable Bowel Syndrome — Pylorospasm — Cardiospasm — Biliary Tract Dysfunctions — and Dysmenorrhea.

Clinical Results: Effective in over 92% of cases.

As for Safety: "Side reactions were uncommon, usually no more than dryness of the mouth...."⁴

Each ENARAX tablet contains:

Oxyphencyclimine HCl 10 mg.
Hydroxyzine (ATARAX®) 25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision only in glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.



New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being™

One-at-Bedtime
TRAL 75 mg.
GRADUMET

**NEW "AUTOMATIC"
CONTROL OF
NIGHTTIME
GASTRIC SECRETION**

TRAL[®] 75^{mg.} Gradumet[®]

Built-in timing actually
steps up drug release dur-
ing critical 2-4 a.m. period

Nighttime gastric secretion hits its peak between 2 and 4 a.m. And that's just when Tral 75 mg. Gradumet, taken at bedtime, is releasing most of its anticholinergic. The patient gets most of the medication when he needs it most . . . in the middle of the night. • Thereafter, Tral 75 mg. Gradumet keeps right on working until the patient wakes the next morning, after a refreshing sleep. And since acidity is controlled the night through, the ulcer has a better chance to heal. • Gradumet's built-in timing is dependable, too . . . never affected by coating thickness, pH or other variables.

• In bottles of 50 and 500.



... and when the problem
is functional bowel disor-
der specify new Filmtab[®]

TRALCYONTM

each Filmtab offers 25 mg.
Tral plus 300 mg. ectylurea

® Tral Gradumet — Hexocyclium Methylsulfate in Long-Release Dose Form*, Abbott. *Patent applied for. ®Filmtab—Film-sealed tablets, Abbott.

002207

**NO SPRAIN,
NO STRAIN,
OR LOW
BACK PAIN**

can resist the rapid
relaxant relief of

RELA™

CARISOPRODOL

RELA—SCHERING'S MYOGESIC^X
RELAXES MUSCLE TENSION
FOR MORE ADEPT MANAGEMENT
OF BOTH SPASM AND ITS PAIN



Rela is most useful in the areas where narcotic analgesics are unwarranted and where salicylates are inadequate. Its muscle-relaxant properties are dependable yet significantly free of the limitations or problems often associated with other relaxants.

MYOGESIC: MUSCLE RELAXANT ANALGESIC



Rela relaxes acute muscle spasm

Relief of muscle spasm
(excellent to good effectiveness
in the majority of patients).¹

**Rela provides persistent
pain relief through its relaxant
and analgesic actions**

"Relief from pain was usually
rapid and sometimes dramatic."¹

**Rela provides comfort
free of spasm and pain**

"A number of patients
reported freedom from insomnia
which they attributed to
freedom from pain."¹

1. Kuge, T.: To be published.

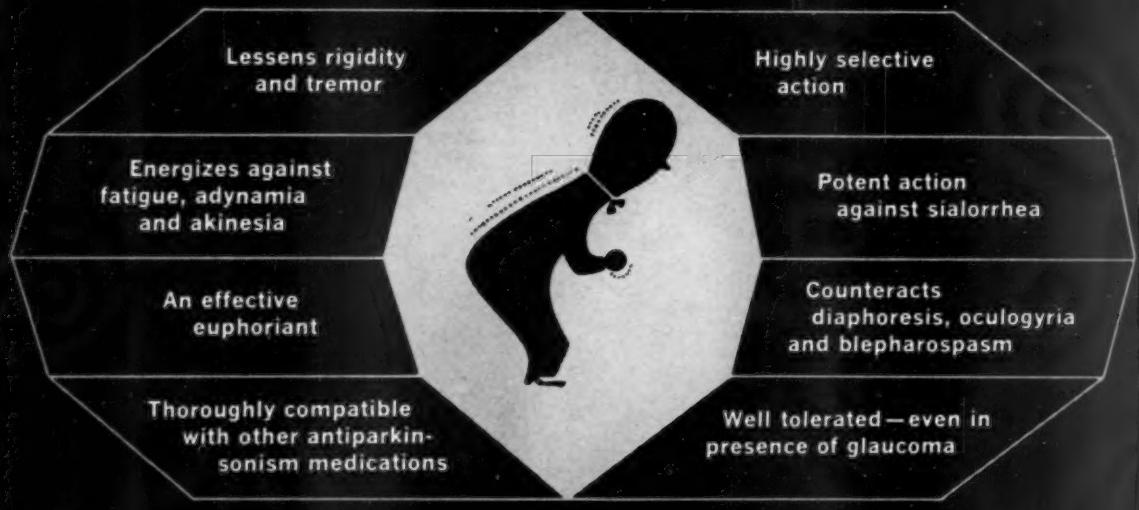
Schering

MULTI-FACETED CONTROL IN PARKINSONISM

REQUIRES

DISIPAL^{®*}

Brand of Orphenadrine HCl



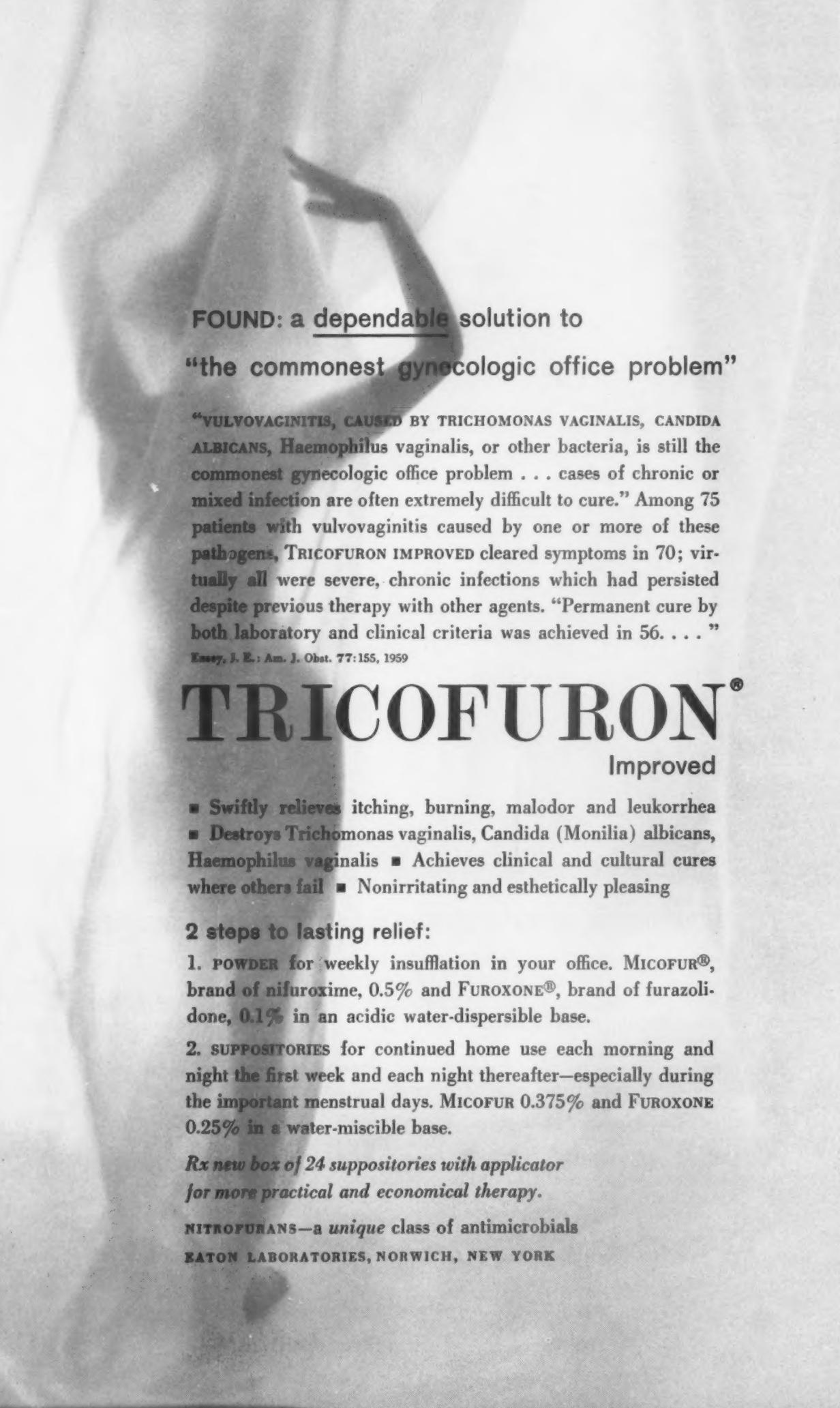
Dosage: Usually 1 tablet (50 mg.) t.i.d.
When used in combination, dosage should be correspondingly reduced.

Bibliography and file card available on request.

* Trademark of Brocades-Sheerman & Pharmacia. U.S. Patent No. 2,567,351.
Other Patents Pending.

Minimal side reactions
Nonsoporific
No known organic contraindications

Riker Northridge, California



**FOUND: a dependable solution to
"the commonest gynecologic office problem"**

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . ."

Ensey, J. E.: Am. J. Obst. 77:155, 1959

TRICOFURON® Improved

- Swiftly relieves itching, burning, malodor and leukorrhea
- Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing

2 steps to lasting relief:

1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.
2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

*Rx new box of 24 suppositories with applicator
for more practical and economical therapy.*

NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK



Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.

*for functional disorders of menopause...
cardiac neuroses...
interval treatment of headache*



BELLERGAL®

*effectively relieves distress of
hot flashes • sweating • headache
• excessive fatigability
• irritability • palpitation • insomnia*

"A double blind study shows that the integrative action of . . . Bellergal Spacetabs is well suited for the symptomatic treatment of patients with vasomotor symptoms. Excellent to good results were achieved in 78 per cent of all complaints in all ambulatory patients treated with Bellergal Spacetabs . . . Symptoms of autonomic instability in patients with psychosomatic disorders alone, in those in the menopause, or in those in whom it was concomitant with organic disease were well controlled." Bernstein, A. and Simon, F.: *Angiology* 9:197, August 1958.

BELLERGAL SPACETABS — Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg.
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS — Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg.
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.



"RISTOCETIN IS AN EFFECTIVE PRIMARY AGENT IN STAPHYLOCOCCAL INFECTIONS"

SPONTIN®

(Ristocetin, Abbott)

CONCLUSIONS—“Ristocetin is an effective primary agent in staphylococcal infections, as well as in short-term therapy of enterococcal endocarditis. It is administered intravenously; intermittent, rapid infusion is recommended. Ristocetin is bactericidal in concentrations attained by this technique . . .

The hematological and other side effects such as phlebitis, skin eruptions, and fever are infrequent with the recommended dosage schedules and mode of administration. The dosage of ristocetin is reduced in renal insufficiency since the antibiotic tends to accumulate.”



INDICATIONS: Against staph-, strep-, pneumo- and enterococcal infections. A drug of choice for serious infections caused by organisms that resist other antibiotics. **DOSAGE:** Administered intravenously. A dosage of 25 mg./Kg. daily will usually be adequate for strep-, pneumo- and enterococcal infections. Most staphylococcal infections will be controlled by 25 to 50 mg./Kg. daily. **SUPPLIED:** In vials containing a sterile, lyophilized powder, representing 500 mg. of ristocetin A activity.



1. Romansky, M. J., Ristocetin, Antibiotics Monographs, No. 12, New York, Medical Encyclopedia Inc., 1959.

REFLECTION ON CORTICOThERAPY:



Particularly in corticotherapy, the intent is not to treat diseases, but to treat patients. This intent is best served by using the steroid that has the best ratio of desired effects to undesired effects:

Medrol*

the corticosteroid that hits the disease, but spares the patient

Upjohn

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

*TRADEMARK, REG. U. S. PAT. OFF. — METHYLPReDnisOLONE, UPJOHN



Full-Time Corrective Action

in mild depression
and chronic fatigue

Deaner®

tablets deanol acetamidobenzoate

Improves *night-time* restoration and *day-time* performance

- Gradually prepares patient to awaken better rested and more alert
 - ...permits sounder sleep
 - ...lessens sleep requirements
- Increases daytime energy
- Counteracts mild depression
 - ...acts to stabilize emotionally disturbed patients with or without concomitant disease
- Useful in treating children with learning defects and behavior problems...lengthens attention span
- Unlike monoamine inhibitors. It is not necessary to monitor Deaner's administration with repeated laboratory tests...Deaner may be given with safety to patients with previous or current liver disease, kidney disease or infectious diseases.

'Deaner' is supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol as the *p*-acetamidobenzoic acid salt.

In Mild Depression

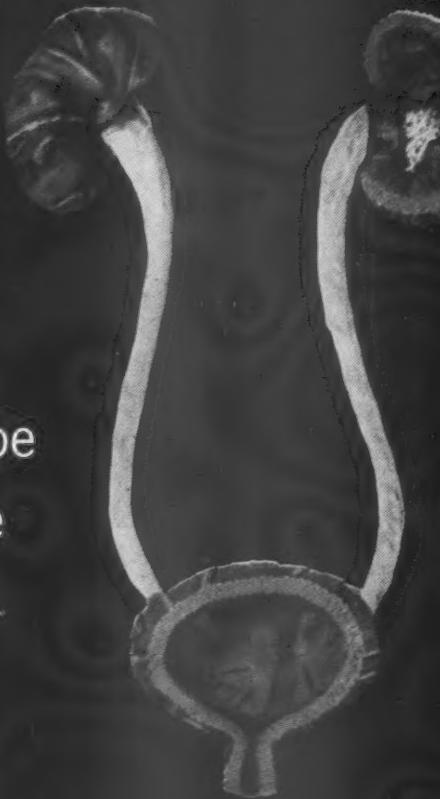
chronic fatigue and many other emotional and behavioral problems

Literature, file card and bibliography on request

Riker

Northridge,
California

Just a "simple" case of cystitis may be the precursor of pyelonephritis¹—or may actually be the first evidence of a pre-existing pyelonephritic process.²



WHEN TREATING CYSTITIS—SPECIFY

FURADANTIN®

brand of nitrofurantoin

to ensure rapid control of infection throughout the urogenital system

FIRST

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
- negligible development of bacterial resistance after 8 years of extensive clinical use
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

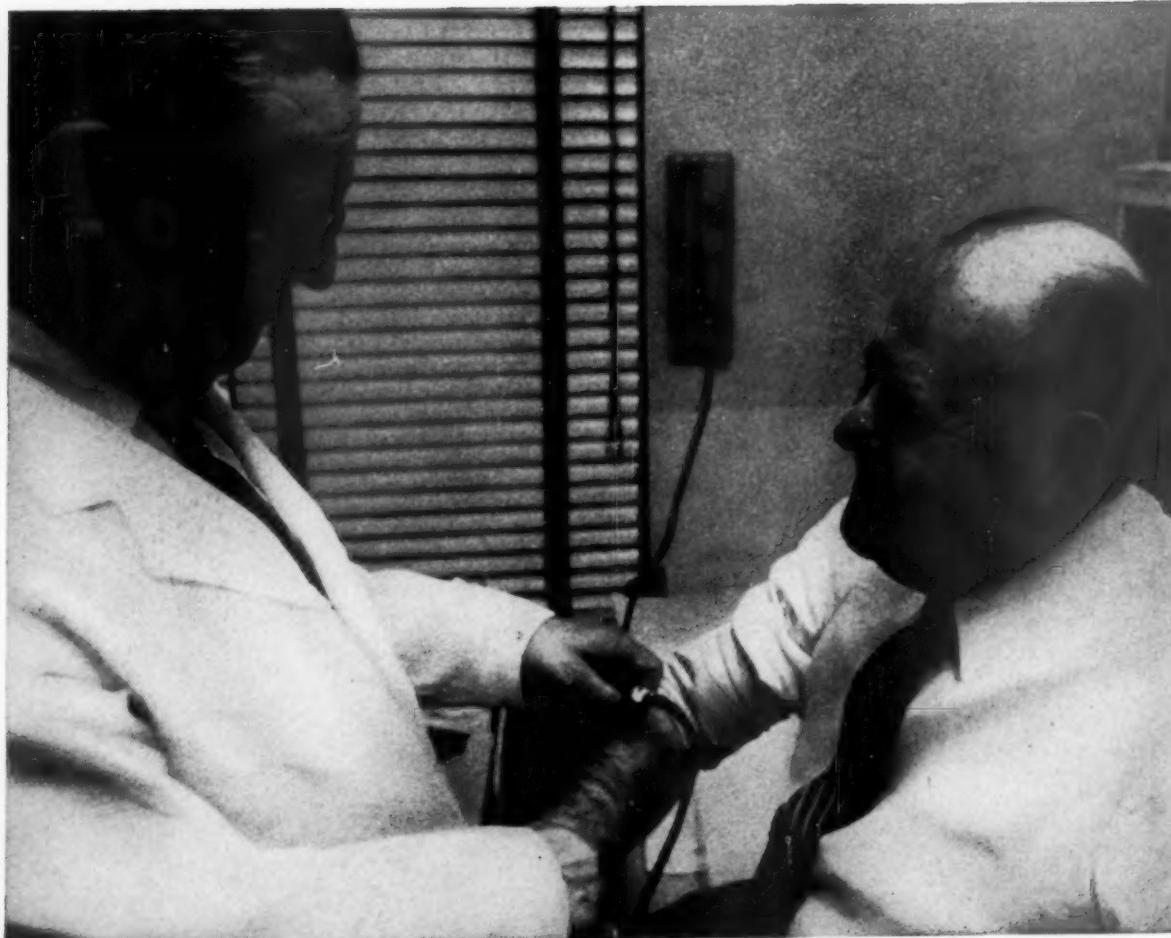
AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

Why so many hypertensive patients prefer **Singoserp**:



2/2782MK

C I B A
SUMMIT, N. J.

It spares them the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."¹

Almost all side effects relieved when Singoserp was substituted for other rauwolfia derivatives in 24 patients²

Side Effects	Incidence with Prior Rauwolfia Agent	Relieved by Singoserp	Not Relieved*
Depression	11	10	1
Lethargy or fatigue	5	5	0
Nasal congestion	7	7	0
Gastrointestinal disturbances	2	0	2
Conjunctivitis	1	1	0

*Two of the 24 patients had two troublesome side effects.

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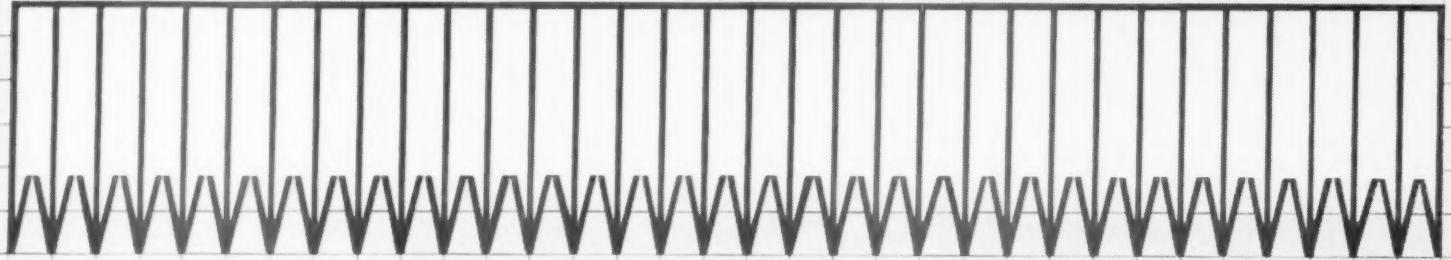


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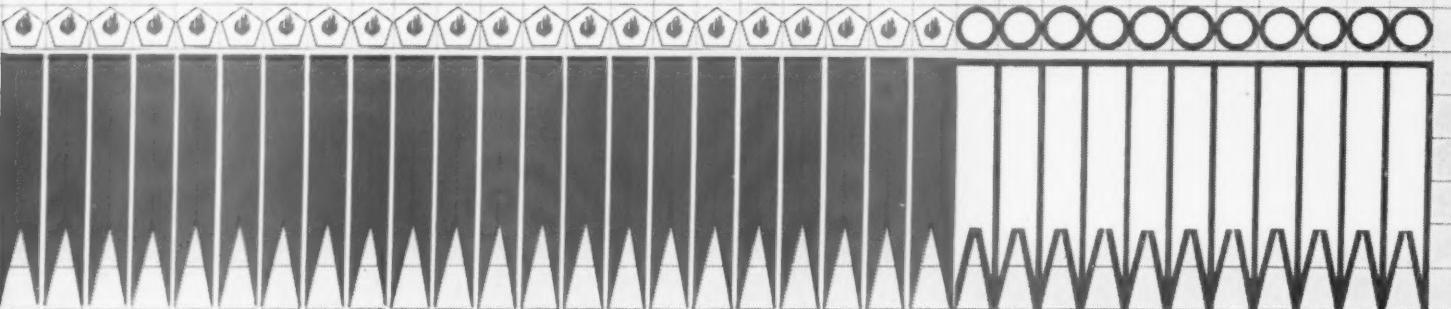
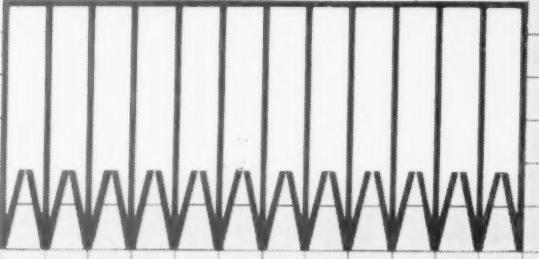
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1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

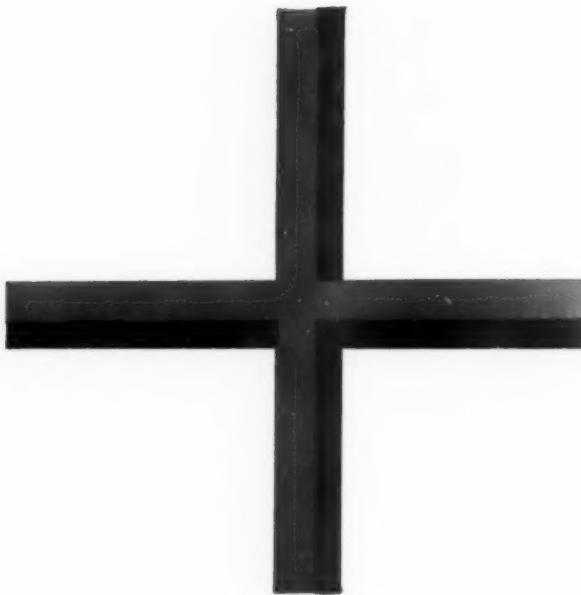
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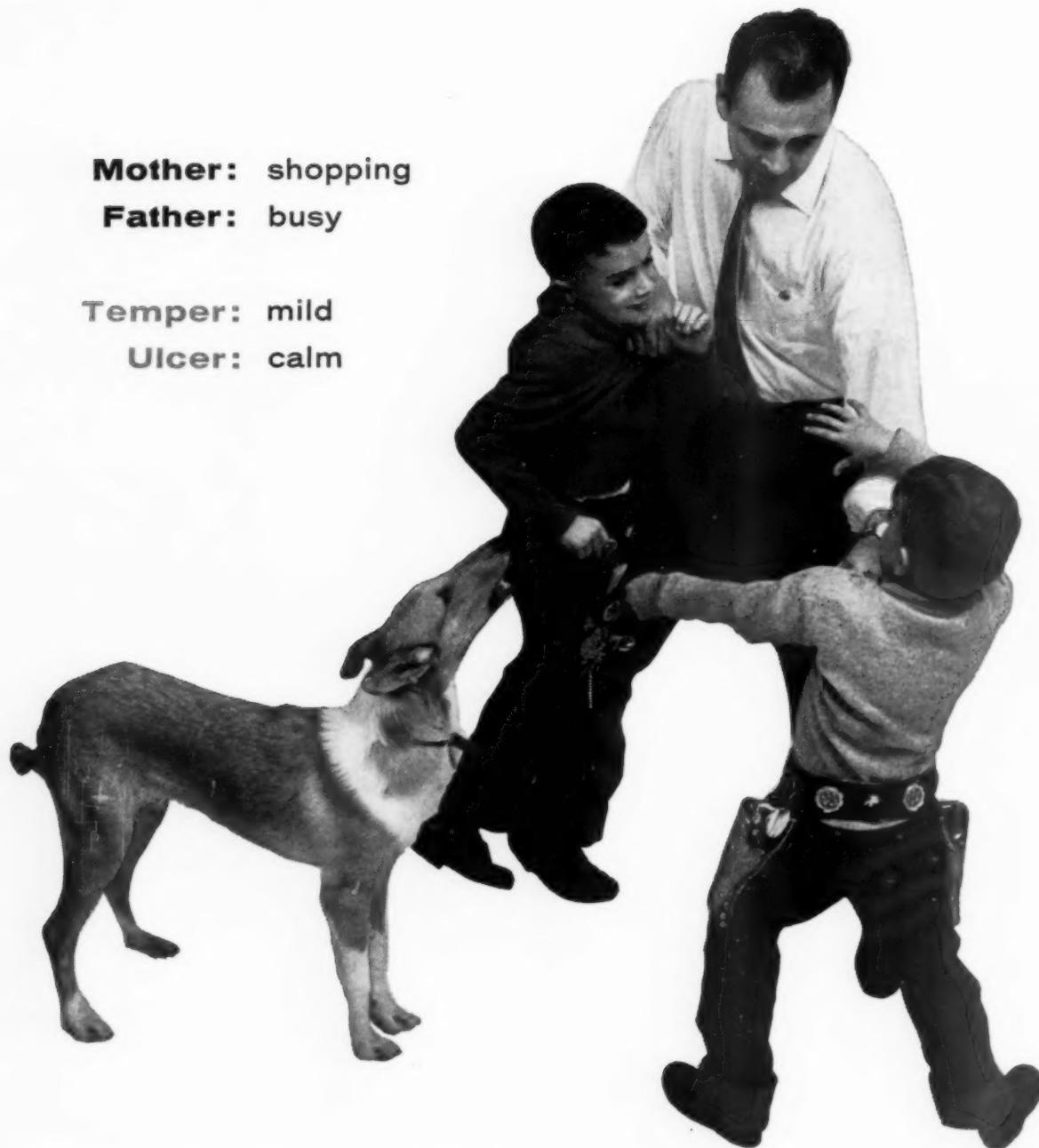
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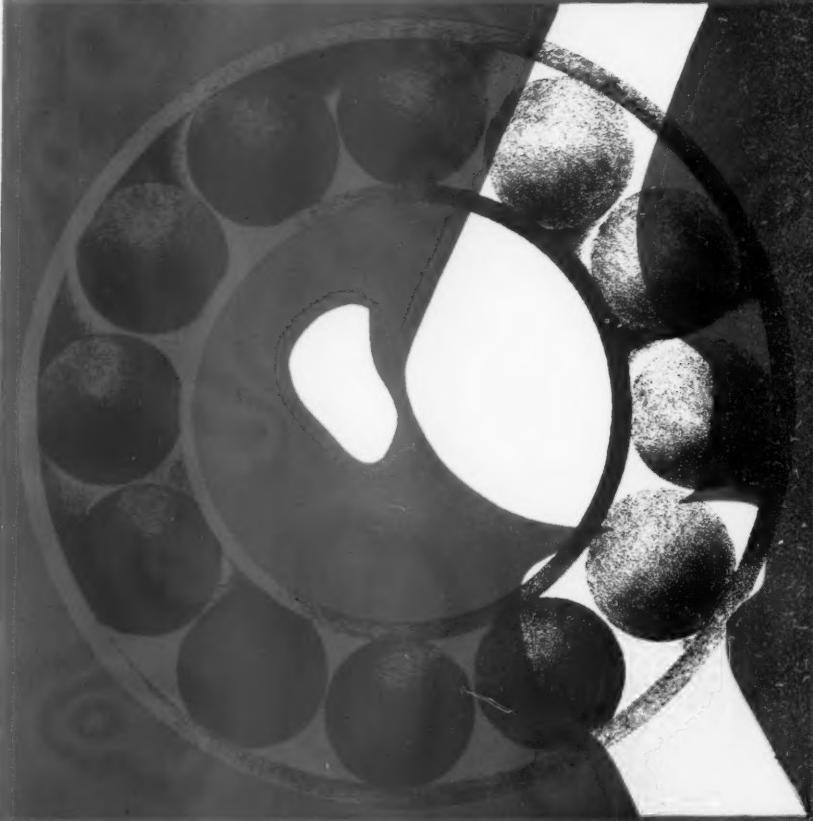
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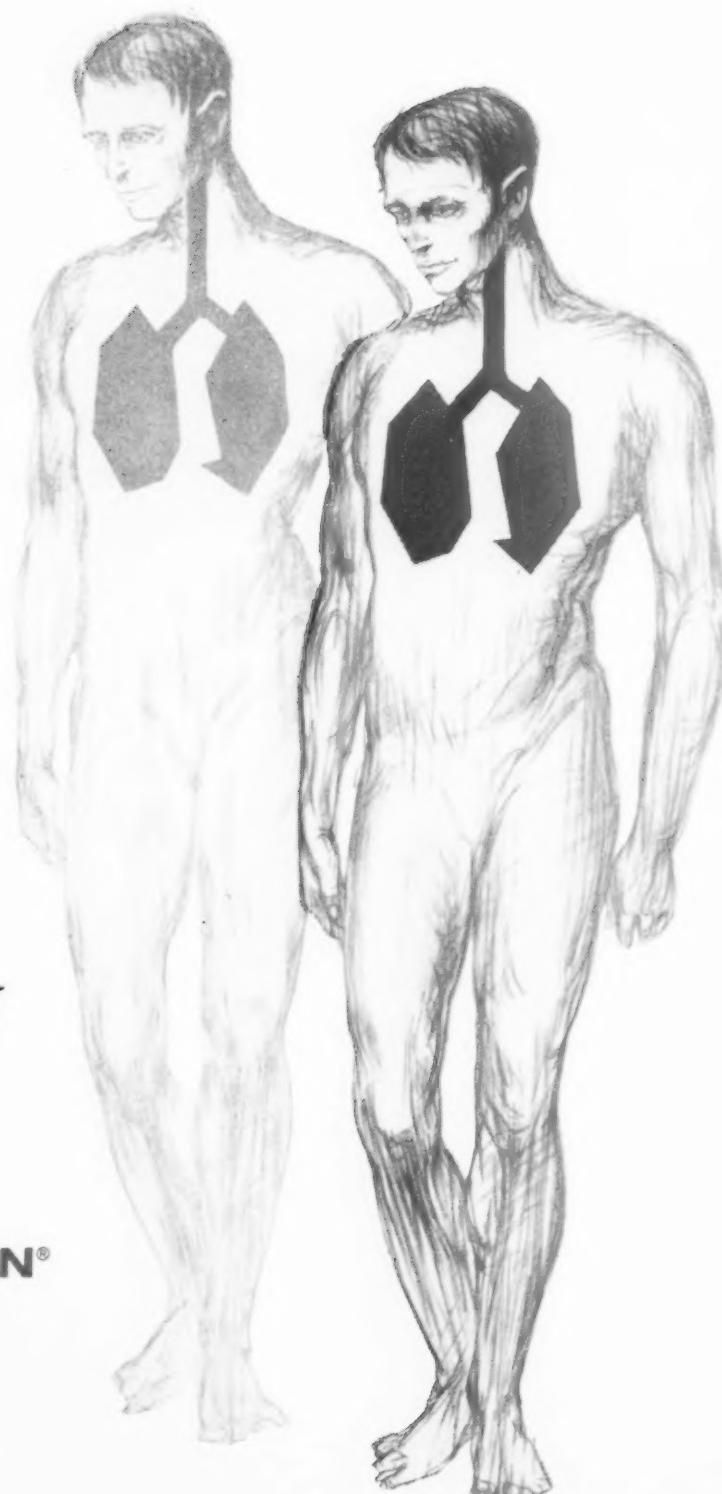
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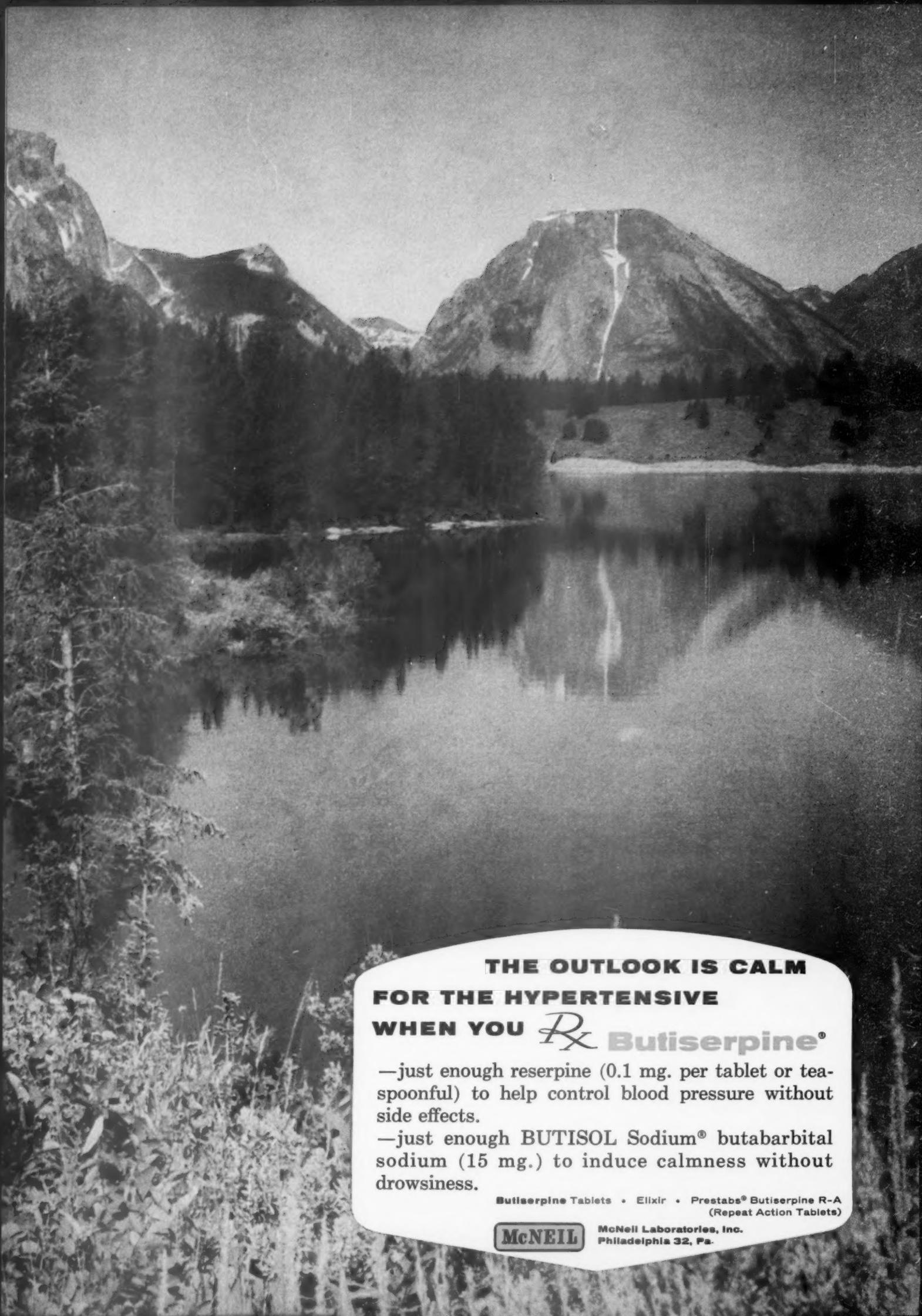
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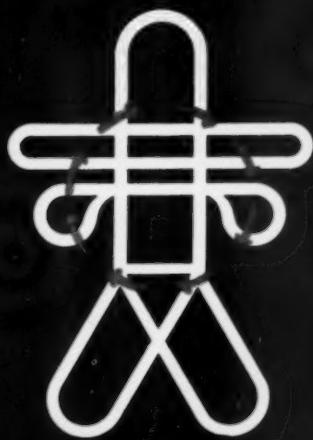
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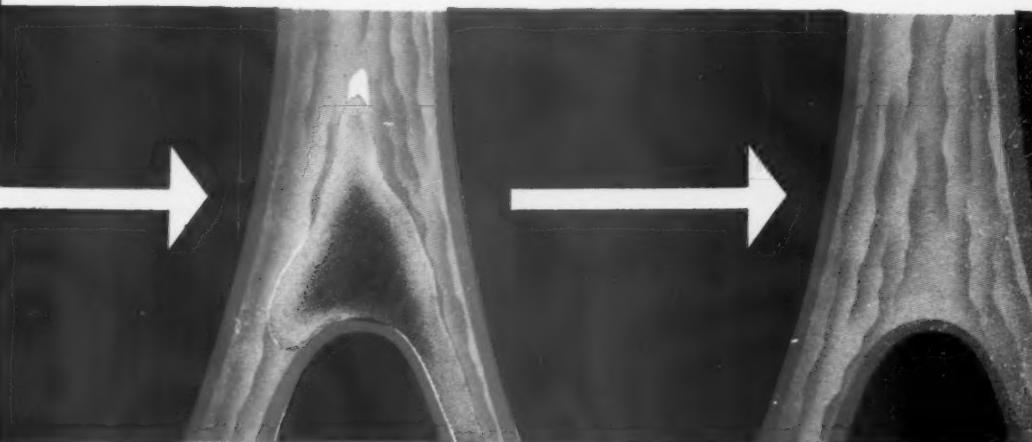
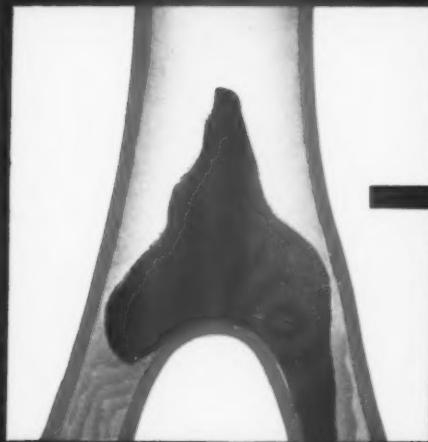


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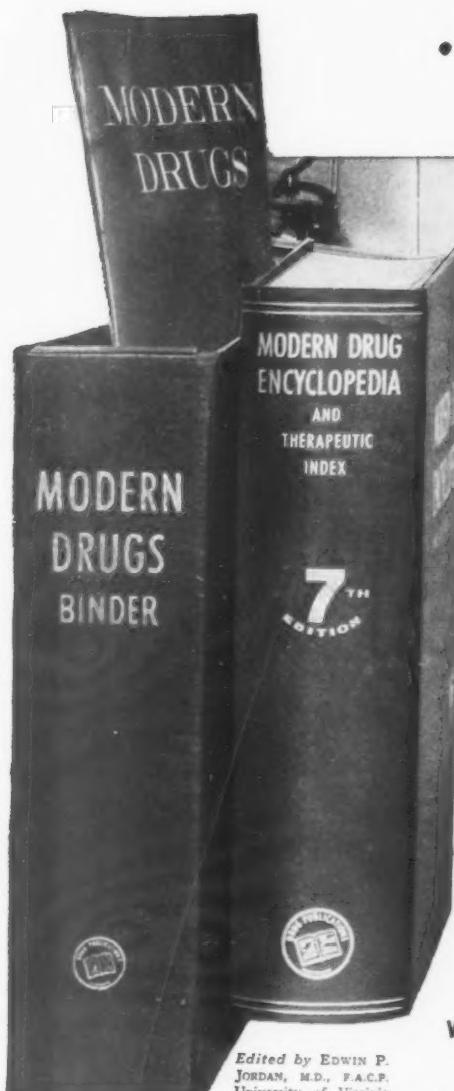
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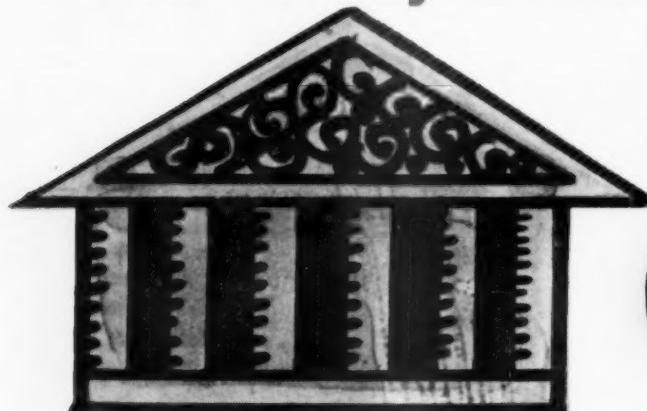
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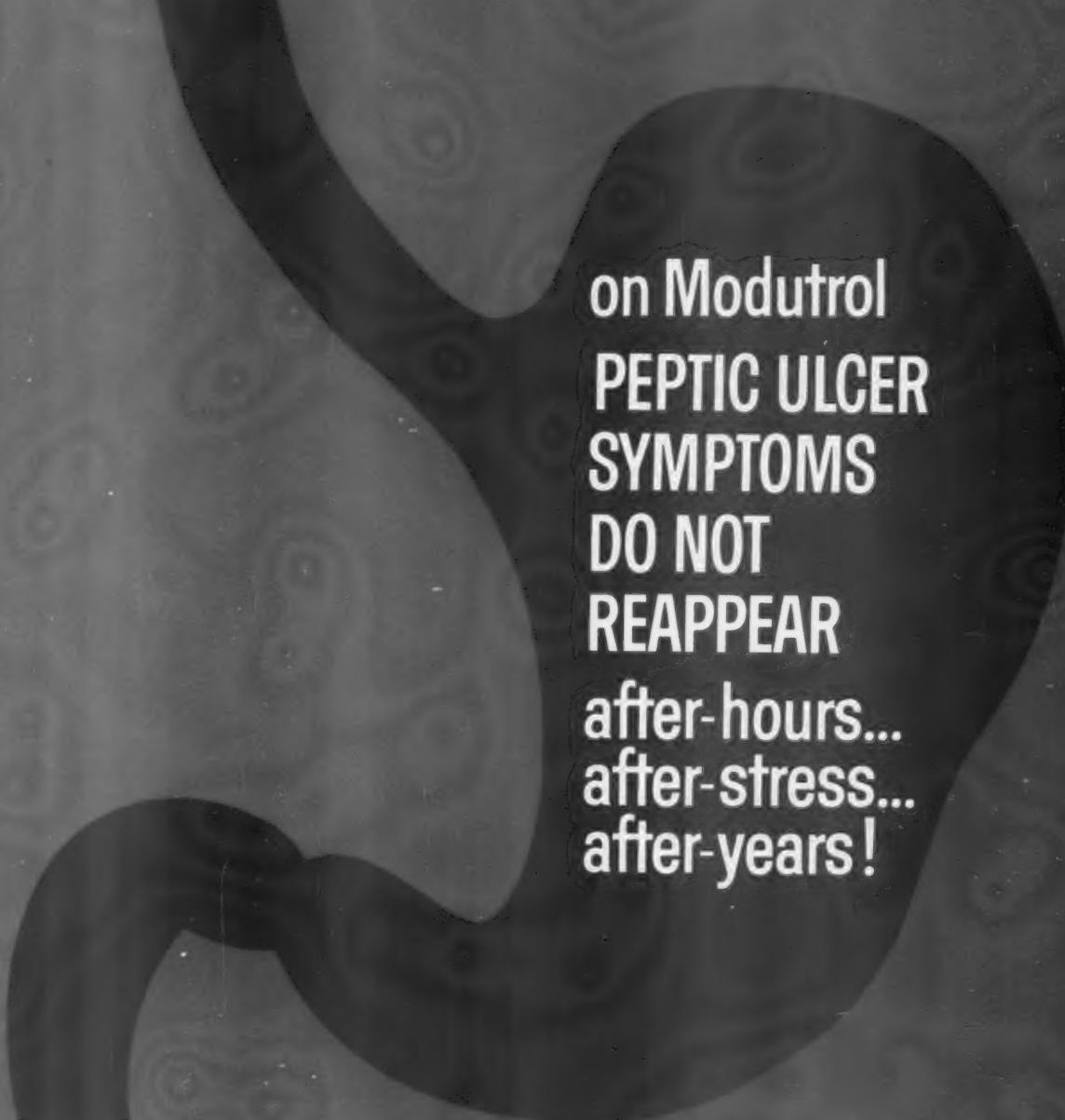
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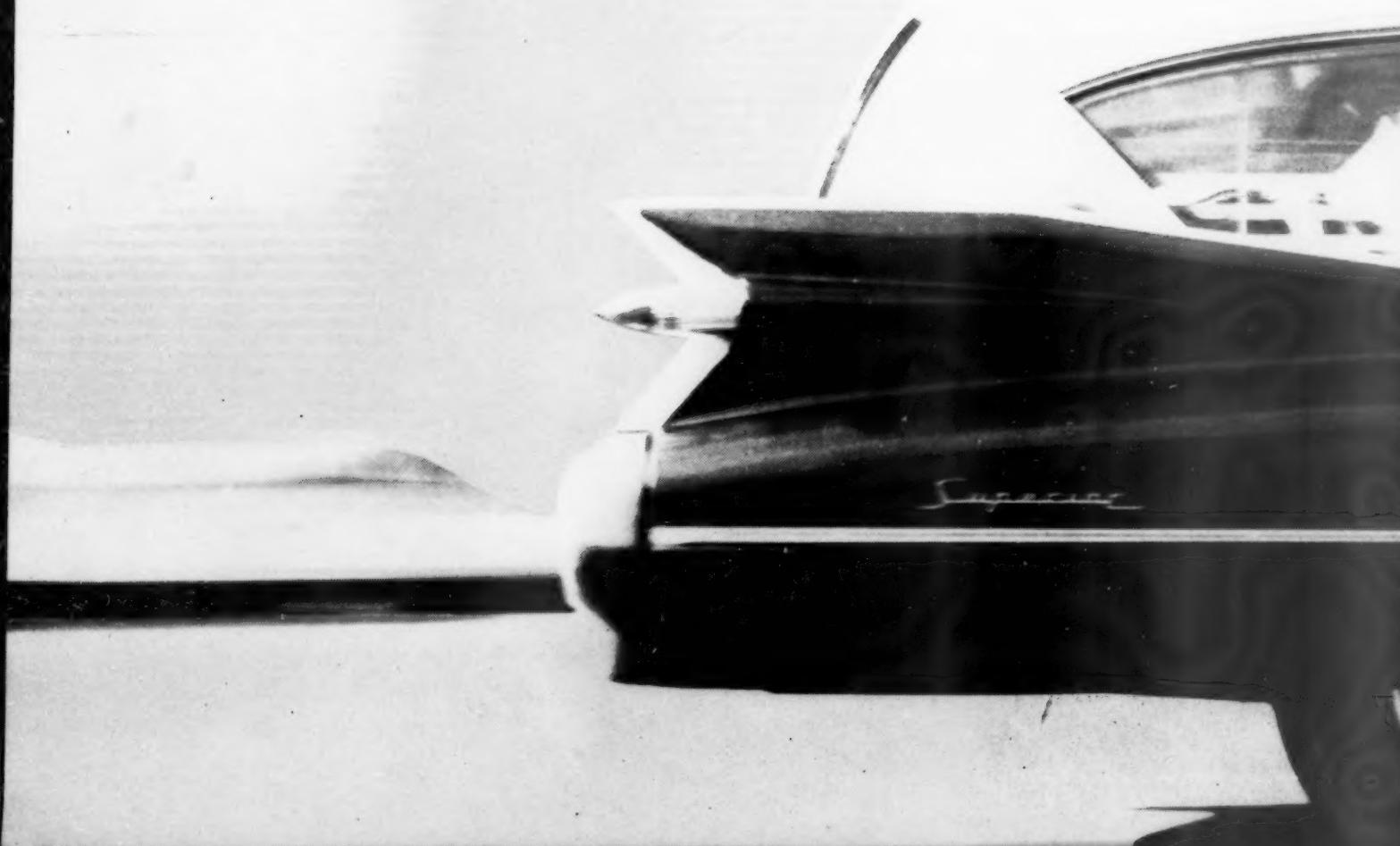
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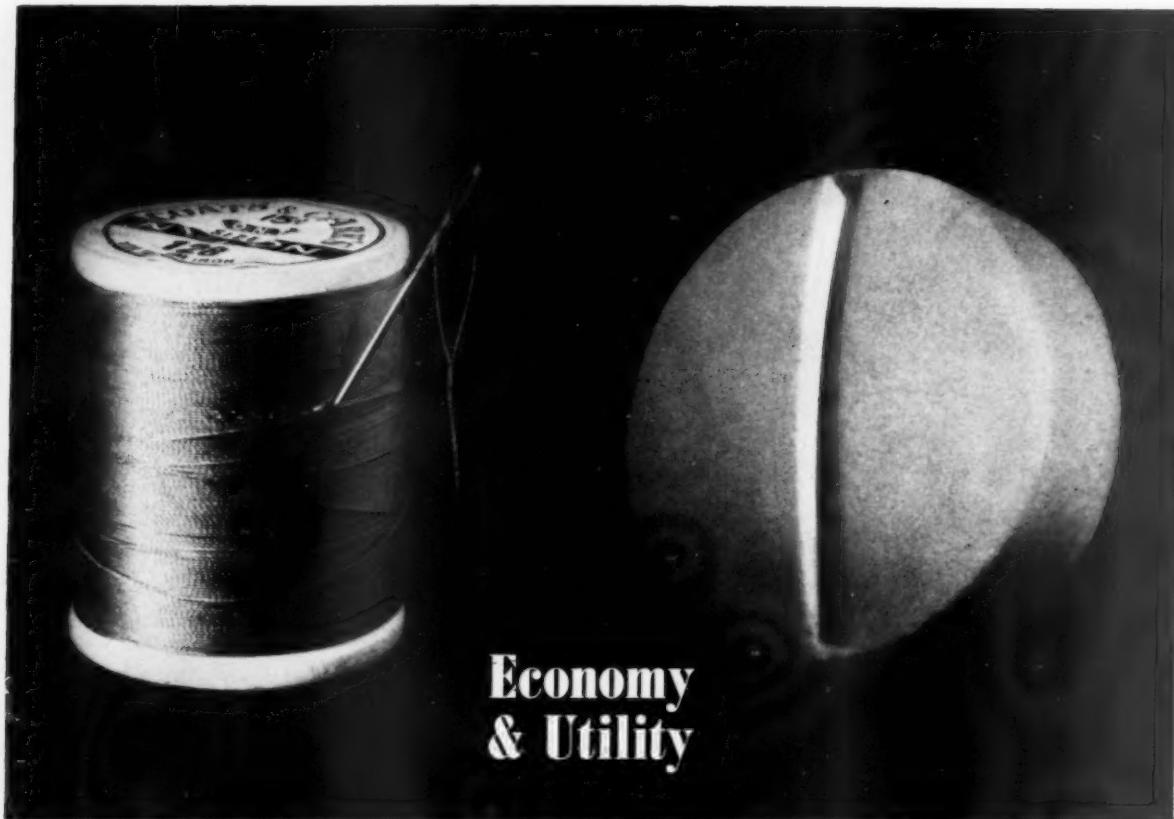


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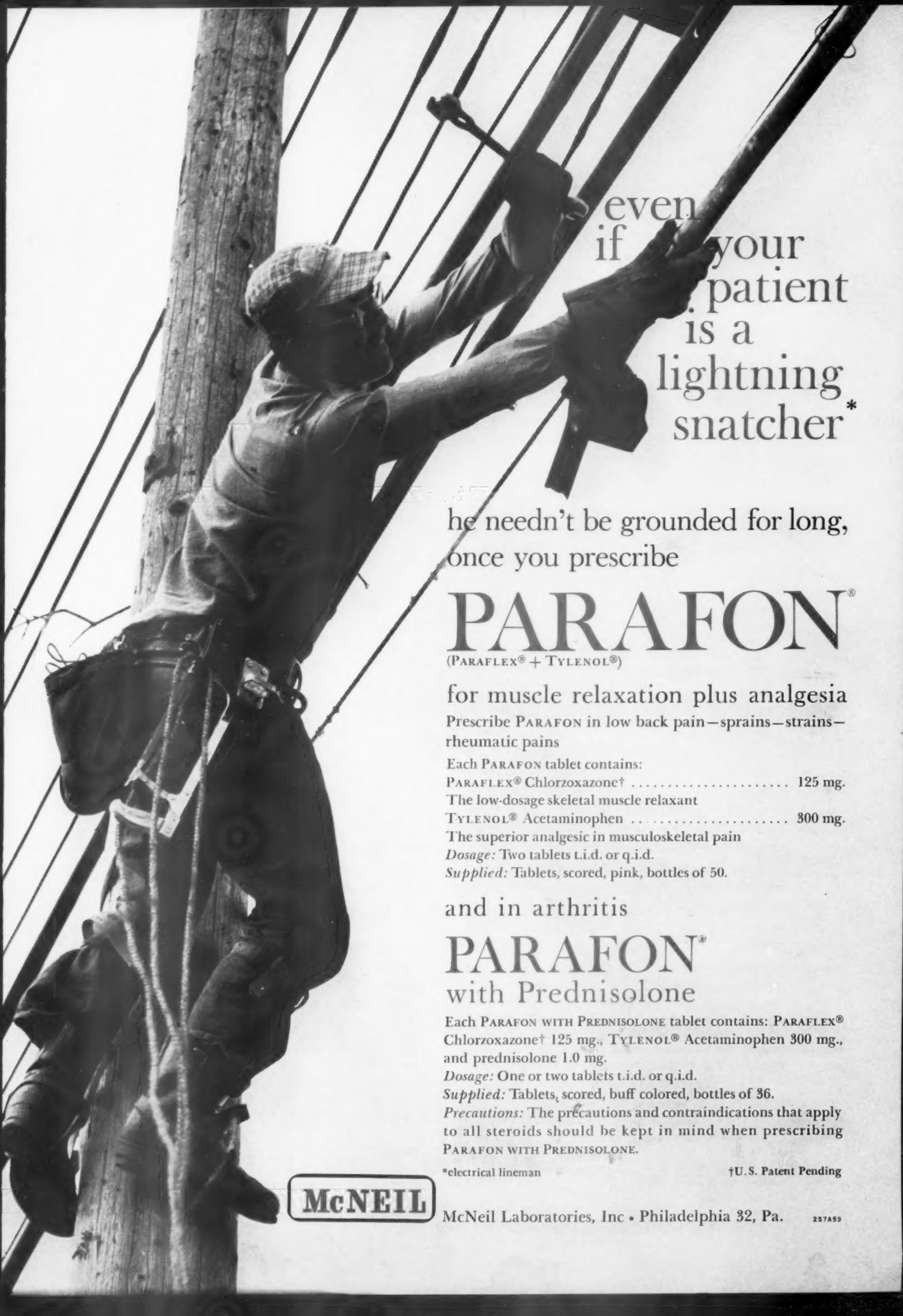
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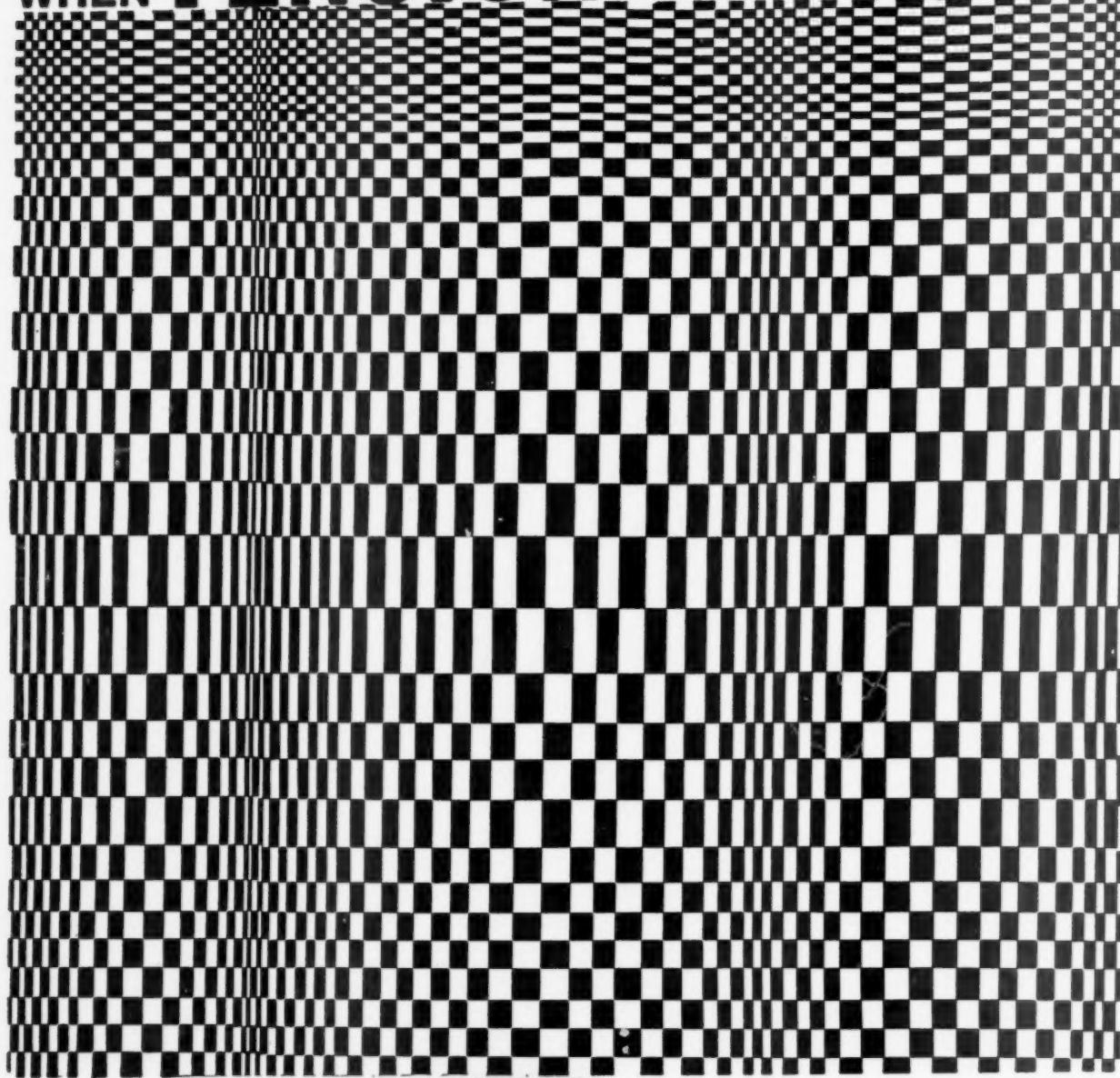


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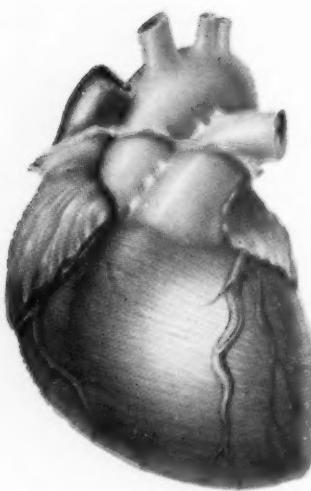
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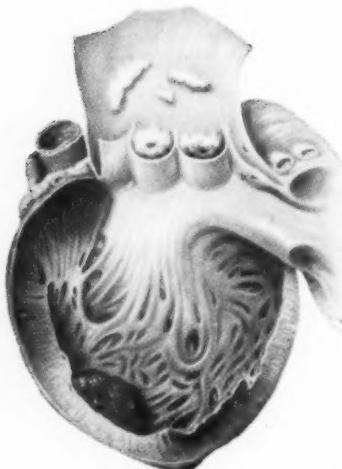
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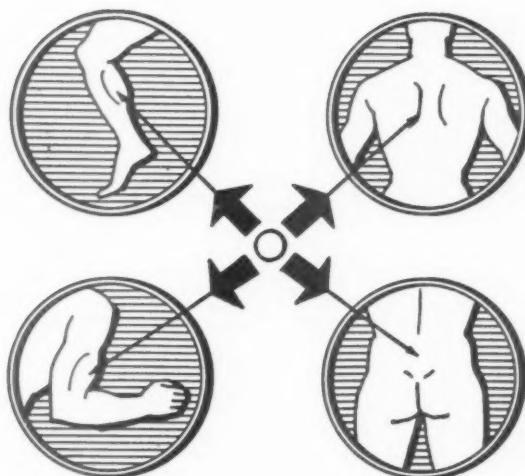
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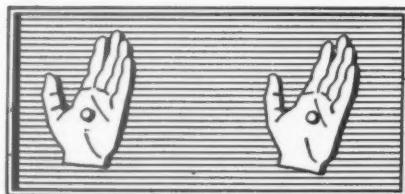
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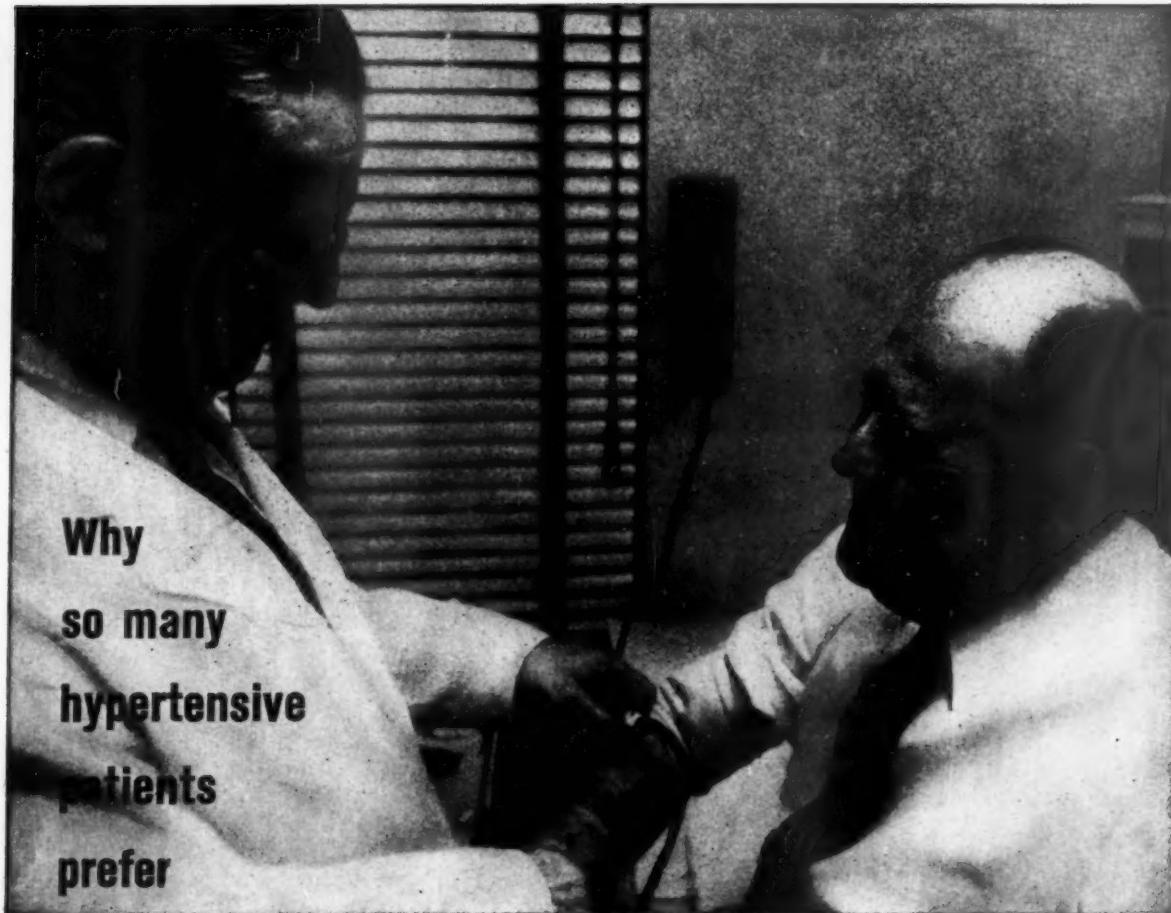
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